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American Heart Journal

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Editorial

THE NEPHROTIC SYNDROME

THE swollen proteinuric child is a continually exciting challenge, for he seems to offer the answers to many metabolic mysteries. Dropsy is, of course, the most conspicuous feature of this strange disorder, the chief cause of parental concern and, therefore, the most tempting therapeutic target. It probably develops because the renal tubule resorbs brine at an excessive rate in an effort to expand blood volume, but the linkage between hypovolemia and sodium retention is quite obscure. The much-discussed volume receptors are still elusive, and all the mechanisms that influence the tubular transport system for sodium are by no means understood. Whereas diuresis from ACTH or from corticosteroids seems to be accompanied by diminished renal output of aldosterone, the meaning of this is obscure, to say the least, since patients with aldosterone-secreting tumors are hypernatremic but not edematous.

In any event, the thoughtful physician will not feel too complacent if his anti-antidiuretic measures are successful because significant disturbances in protein metabolism precede, and probably evoke, water retention. The pathogenesis of hypoalbumenemia is not understood. Some investigators attribute it entirely to the proteinuria, whereas others consider this explanation inadequate because the rate of protein synthesis in nephrosis is often greatly increased and the quantity of protein excreted is relatively small. Evidence of heightened protein catabolism has been found both in nephrosis and in idiopathic hypoproteinemia so that protein destruction and protein loss may both contend in variable proportions with protein synthesis in determining the concentration of protein in the plasma. There is reason to think that the kidney may destroy, as well as excrete, protein. The lipemia of nephrosis may be related to a lipid-mobilizing factor recently isolated from the plasma of animals treated with cortisone by Seifter and his colleagues. It would be surprising, indeed, if the nephrotic syndrome does not prove to be of endocrine origin.

Older clinicians, confronted with the combination of edema, proteinuria, hypoalbuminemia, and lipemia, were apt to return a diagnosis of glomerulonephritis whether there was a history of hematuria or not, especially if the patient was also hypertensive and azotemic. It is currently fashionable, however, to divide the problem into Type I and Type II nephritis after the manner of Ellis

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(1942), who suggested that the patient with postinfectious hematuria, hypertension, and edema differs fundamentally from the one whose illness begins insidiously with hypoproteinemic edema. Americans may feel that these categories should be entitled Type A and Type B, after Longcope, who had arrived at the same conclusions in 1936. Wider employment of the biopsy needle has further emphasized the large number of renal lesions that accompany the nephrotic syndrome. Kark and his collaborators, who have probably done more renal biopsies than any other team in this country, permit me to say that in fifty-six cases with the nephrotic syndrome the diagnoses on punch biopsy material were:

Subacute glomerulonephritis (membranous or proliferative)	16	
Diabetes mellitus	12	
Systemic lupus erythematosus (lupus nephritis)	10	(3 had pseudonephrotic syndrome)
Nephrotic syndrome with predominant tubular degeneration	6	
Chronic glomerulonephritis	3	
Renal vein thrombosis	2	(1 case not diagnosed by renal biopsy)
Primary amyloidosis	1	
Normal (biopsies made after diuresis)	3	
Inadequate	2	
Diagnosis Uncertain	1	

Whereas new tissue stains emphasize the great frequency of abnormalities in the basement membrane of the glomeruli, some cases have exhibited no structural changes. It is possible that thickening and splitting of the membrane is due to prolonged filtration of certain globulins. Continuing work with nephrotoxic serum seems to show that it can, under conditions not yet well defined, produce either a proliferative glomerulitis resembling that seen in human hemorrhagic nephritis or the basement membrane thickening, which may be the common denominator in the miscellaneous causes of nephrosis. Crescents and intracapillary thrombi are no longer thought to be pathognomonic of the former disease, and the latter lesion often leads to glomerular obliteration and malignant hypertension. Although it is generally agreed that the glomerular lesions cause the proteinuria, defective tubular transport of filtered protein also contributes to the total deficit, since in the normal human being this probably amounts to 50 to 60 Gm. daily. Present nomenclature is unsatisfactory, but it may be well to reserve the term lipoid or genuine nephrosis for those rare cases with normal glomeruli in which the prognosis is thought to be good, but this information is available only to the pathologist. The clinician will do what he can to identify such special causes of the nephrotic syndrome as disseminated lupus erythematosus, amyloid disease and diabetes mellitus, and to the residue is probably justified in attaching the descriptive term membranous glomerulonephritis.

It is well to emphasize the basement membrane thickening, for this is the structure that apparently produces the antigen responsible for the experimental disease. It—and not edema—is the proper therapeutic target. Too little is known of the ability of steroids to modify this lesion, but adequate therapy seems to abolish proteinuria in about half the patients, the remainder faring poorly. Although there is no general agreement regarding details of therapy, accumulating evidence suggests that prolonged intermittent courses of steroids control the glomerular lesions and prolong remissions.

THOMAS FINDLEY, M.D.

Original Communications

A COMPARISON OF FACTORS AFFECTING THE HIGH-FREQUENCY (STARR) AND THE LOW-FREQUENCY, CRITICALLY DAMPED (NICKERSON) BALLISTOCARDIOGRAPHS WITH SPECIAL REFERENCE TO AGE AND BODY DIMENSION

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OF THOSE factors which are known to affect the ballistocardiogram of the normal male, there is unanimous agreement that regardless of the type of recording instrument employed age is accompanied by a declining IJ amplitude. Trends in IJ amplitude or derived functions such as stroke volume have been found by investigators in several laboratories using the high-frequency Starr type apparatus.[1-3] The effects of age have been studied by two investigators using the low-frequency critically damped ballistocardiograph designed by Nickerson.[4,5] While age changes of the same order of magnitude were found, no adequate information is available to define which instrument is most sensitive to the effects of age. An important aspect of the relationship of age to the ballistocardiograph is the increase in the number of apparently abnormal patterns with increasing age recorded by both the Starr instrument[3] and the body pick-up device introduced by Dock.[6] However, this relationship will not be examined in this communication.

The relationship between ballistocardiographic amplitude and/or stroke volume and the measures of body size are not so clear. For example, Tanner[7] published correlation coefficients based on his own and Starr's observations that demonstrated little or no relationship between surface area and calculated cardiac output or stroke volume. On the other hand, evidence[8] was provided to show that the low-frequency critically damped apparatus of Nickerson gave a relatively large correlation coefficient between surface area and cardiac output. Similar discrepancies were found between the correlation coefficients relating

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IJ amplitude and measures of body dimensions. Scarborough and associates,[3] using the high-frequency apparatus, could find no relationship between IJ amplitude and height, weight, or surface area in the 261 apparently normal males and 108 apparently normal females who were studied in the Baltimore laboratory. In this laboratory,[5] it has been shown that when the low-frequency critically damped apparatus of Nickerson is employed, the IJ amplitude of normal young men is related to body weight, body height, and surface area by correlation coefficients which are significantly different from zero. But in middle-aged men the correlation coefficient between IJ amplitude and height becomes the most important relationship with the affects of weight becoming insignificant.

It is of some interest to know whether this apparent difference in these two pieces of equipment is due to differences in the physical characteristics of the two ballistocardiographs, to differences in sampling, or to differences in the physiologic conditions under which the work was done. Data are presented in the present paper which are intended to clear up these questions and which will provide a reasonably precise comparison of the effects of age on the IJ amplitude as measured by the high-frequency on the one hand and the low-frequency critically-damped apparatus on the other.

METHODS, CONDITIONS, AND SUBJECTS

A special ballistocardiograph was constructed which allowed recordings to be made with the conditions used by Starr and associates[9] or with the conditions used by Nickerson and associates.[10] The table was equipped with a single stiff spring which could be attached to or disengaged from the foot of the bed. The bed, which weighed 40 pounds, was supported by four soft springs which were mounted on each leg of the table and fitted with clamps to allow changing the effective length of the spring as described by Nickerson and associates.[10] The usual oil damper fitted with a plunger was used to provide critical damping for the Nickerson ballistocardiogram. The high-frequency or Starr type ballistocardiogram was taken with the stiff spring attached to the bed, the plunger removed from the oil damper, and the soft springs clamped at a standard setting. Under these conditions, the natural frequency of the bed with a dead weight of 150 pounds was found to be 9.8 cycles per second. With the stiff spring disengaged, the bed could easily be calibrated to give 1.5 cycles per second and set for critical damping for a wide range of weights and temperatures.

This apparatus made it possible to obtain consecutive high- and low- frequency ballistocardiograms on the same individual without disturbing the circulation. The type of ballistocardiogram made first was alternated from subject to subject. The majority of the subjects reported to the laboratory without breakfast. A few of the younger men were allowed to have their ballistocardiograms 4 hours after breakfast. Before mounting the ballistocardiographic table, the subjects sat in a chair for 20 minutes. They rested on the table for 10 minutes before any tracings were made. The ballistocardiograph was located in an air-conditioned room the temperature of which was kept at 78° F. with a relative humidity of 50 per cent.

TABLE I. CHARACTERISTICS OF 51 YOUNG (AGE 18 TO 26) AND 57 MIDDLE-AGED (AGE 50 TO 59) MALE SUBJECTS ALONG WITH THE BALLISTOCARDIOGRAPHIC DATA OBTAINED ON THEM

GROUP		AGE	HT. (CM.)	WEIGHT (KG.)	MEAN BLOOD PRESSURE	LOW FREQUENCY BCG			HIGH FREQUENCY BCG		
						PULSE	AMPLITUDE	S. V.	PULSE	AMPLITUDE	S. V.
Young men:	Mean	22.2	177.5	75.33	98.37	61.50	51.74	100.76	61.85	526.6	109.5
	S. D.	2.85	6.74	11.78	7.63	8.20	11.89	20.12	9.01	128.68	14.48
Middle-aged men:	Mean	54.03	175.3	74.94	96.65	58.12	33.44	74.31	58.86	373.79	88.57
	S. D.	2.78	6.70	11.28	6.74	6.51	8.16	15.08	6.27	81.32	12.25

Two groups of subjects were studied. A young group of 51 college students aged 19 to 29 and a middle-aged group of 57 Twin City business men aged 50 to 59. Both groups were examined in the laboratory and only those who were free of disease detectable by physical examinations were included. In addition, it was required that the men have a blood pressure of less than 140/90, a normal electrocardiogram, and a normal heart size as judged by a radiologist from a six-foot x-ray of the chest.

The middle-aged men were selected from the large group under study in this laboratory[5] by inspection of the high-frequency ballistocardiogram pattern. The first 57 men visiting the laboratory in 1954 who had normal ballistocardiogram patterns were employed in the study. It was found as a general rule that when the high-frequency pattern was normal, the low-frequency pattern was classified as typical of the pattern found in young men.

With both pieces of equipment, static calibrations were used and applied to the records of each individual. Amplitudes of the IJ complexes were calculated in terms of the gravitational force (grams) necessary to produce the observed displacement. The high-frequency bed was calibrated by calculating the means of 4 displacements produced by 317.3 grams of weight and the Nickerson bed was calibrated with 8 displacements produced by a 50 gram weight. In the high-frequency record, both the area and the amplitudes of the I and J waves were measured in 2 of the largest and 2 of the smallest complexes in a respiratory cycle. In the Nickerson record, IJ amplitudes were measured in each complex in a complete respiratory cycle. "Stroke Volumes" were calculated from the high-frequency records by Starr's area formula as revised by Tanner[7] and from the low-frequency records by the formula given by Nickerson and associates.[10]

RESULTS

The means and standard deviations of some of the characteristics of the subjects along with the ballistocardiographic observations on the two groups are presented in Table I. The correlation coefficients between the IJ amplitude and measurements of body size are presented in Table II. It will be noted that the correlation coefficients between IJ amplitude and height are significantly larger than zero at all ages with both ballistocardiographs. On the other hand, the correlation coefficients between IJ amplitude and weight are significantly different from zero when the amplitude is determined with the low-frequency equipment but not with the high. The correlation coefficients between IJ amplitude and surface area lie, as one might expect, between these two extremes. The significance of the differences between the several sets of correlation coefficients were tested.

It was found that in young men that the correlation coefficients between IJ amplitude and weight and IJ amplitude and surface area obtained with the low-frequency ballistocardiograph were significantly larger than those obtained with the high-frequency equipment. The probability that both these differences could occur by chance was found to be less than 2 in a 100. While the other differences between correlation coefficients obtained with the two instruments were not statistically significant, it should be mentioned that the cor-

relation coefficients in the older age group between IJ amplitude obtained with high-frequency instrument and both body weight and surface area were consistently smaller than those obtained with the low-frequency ballistocardiograph. It is clear that if one was to pick a body dimension which could be used to construct normal standards, height would be the dimension of choice for both the high- and low-frequency ballistocardiograms.

TABLE II. A COMPARISON OF THE IJ AMPLITUDES OBTAINED WITH THE HIGH-FREQUENCY (STARR TYPE) AND LOW-FREQUENCY (NICKERSON) BALLISTOCARDIOGRAPHS: THE CORRELATION COEFFICIENTS BETWEEN IJ AMPLITUDES AND BODY DIMENSIONS

ITEMS CORRELATED	YOUNG MEN		MIDDLE-AGED MEN	
	LOW FREQUENCY	HIGH FREQUENCY	LOW FREQUENCY	HIGH FREQUENCY
IJ amplitude and height	0.60	0.55	0.51	0.53
IJ amplitude and weight	0.55	0.18	0.33	0.13
IJ amplitude and S. A.	0.65	0.32	0.42	0.27

The significance of the values of r:
The probability that r is different from zero is for the young men 1% r = 0.361
5% r = 0.279
for middle-aged men 1% r = 0.337
5% r = 0.260

Elsewhere[5] it has been shown that combining height with weight and/or surface area to calculate multiple correlation coefficients does not improve the correlation between height and the IJ amplitude of the low-frequency critically damped ballistocardiogram. Similar calculations were made with the high-frequency IJ amplitude and no multiple correlation coefficient was found that was larger than the correlation coefficient between IJ amplitude and height.

Since regression equations, relating IJ amplitude and the several body dimensions for the low-frequency, critically damped ballistocardiogram, have been presented elsewhere,[5] only equations for the high-frequency ballistocardiogram are presented here and these are restricted to the relationships between amplitude and height. For young men IJ amplitude may be predicted from the following equation:

IJ amplitude = 10.01 HT (in cm.) − 1250.3, with a standard error of estimate of 109.8.

In middle-aged men the relationship is as follows:

IJ amplitude = 6.54 HT (in cm.) − 756.8, with a standard error estimate of 69.08.

The relationship between the two types of ballistocardiograms was also studied. It was found that the IJ amplitude of the low-frequency ballistocardiogram was related to the high-frequency by a correlation coefficient of 0.62 in young men and 0.61 in the older group. Calculation of the stroke volume from the empirical constants devised by the originators of the methods[9,10] did not

improve the agreement between the two methods. The correlation coefficient between the stroke volumes of the two methods was 0.64 in the young group and in the older group, 0.42.

The effects of age as measured by the two ballistocardiographs are presented in Table III. The low-frequency, critically damped ballistocardiograph recorded a 35 per cent decrease in the IJ amplitude, while the high-frequency equipment showed only a 29 per cent decrease in the same measures. In order to decide whether the age trend recorded by the low-frequency, critically damped ballistocardiograph was in fact larger than that recorded by the high-frequency (Starr type) the following analysis was carried out. A relative deviate for each older individual was calculated according to the expression: $(\bar{x} - y) / S$ where $\bar{x}$ is mean IJ amplitude for the young men with S its standard deviation and y is the observed IJ amplitude for the individual middle-aged man. Relative deviates were calculated for each man in the middle-aged group for the IJ amplitudes obtained with both the high-frequency and low-frequency, critically damped ballistocardiographs. The mean difference between the deviates was 0.352, indicating a larger age increment in the low-frequency, critically damped apparatus. This figure was tested with the T test for pair deviates and the T was found to be 4.54, indicating that the observed difference could occur by chance in less than one occasion in a hundred.

TABLE III. THE EFFECTS OF AGE ON THE IJ AMPLITUDE OF THE HIGH-FREQUENCY (STARR TYPE) AND LOW-FREQUENCY (NICKERSON) BALLISTOCARDIOGRAMS

	IJ AMPLITUDE		△ WITH AGE	% △ WITH AGE	T VALUE
	YOUNG MEN	MIDDLE-AGED MEN			
Low frequency BCG	51.7	33.4	18.3	35	9.41
High frequency BCG	526.6	373.8	152.8	29	7.45*

*Differences between groups are significant at the 1% level if the T value is greater than 2.63.

DISCUSSION

This laboratory is interested in exploring the possibility that the ballistocardiograph may be of some usefulness as a tool to be used in the study of the epidemiology of coronary disease. An important part of such studies consists of comparisons of age trends of biochemical and physiologic characteristics in populations characterized by degenerative heart disease death rates which are widely different.[11,12] It is therefore of some interest to determine which of the currently available ballistocardiographic methods are most sensitive to the effects of age. Direct comparison of the amplitudes recorded by the two instruments are meaningless since the same parameters of the force imparted to the ballistocardiograph bed are not recorded[13,14]; and neither record is free of artefact.[13,14] It was felt that a precise physical basis for comparison could not be

obtained. It appeared to be more practical to compare the age decrements in terms of the relative deviate. In this statistical expression the units of measurement cancel out and the response to age is examined in terms of the capacity to obtain a significant difference between young and middle-aged groups of males.

The fact that significant correlations between amplitude and body dimensions were obtained in this laboratory but not in others is of some interest and should be examined. The use of the oil damper without the plunger and both soft and hard springs in recording the high-frequency pattern should be considered as an explanation. This appears to be unlikely since the characteristics of the body dominate the frequency response characteristics of the high-frequency system. A more likely explanation would appear to lie in the physiologic conditions under which the observations were made. Other investigators have made their observations without reference to the time of the last meal. Paine and Shock[15] have shown that the effect of meals is large and lasts for a considerable time. While the correlation coefficients between height and IJ amplitude are significantly different from zero, the slope of the regression line is not large and it seems quite likely that rigid standardization of the physiologic conditions is necessary if such correlations are to be demonstrated.

It is clear that if either of these ballistocardiographs are to be used in population comparison studies, attention will have to be paid to the body dimensions of two populations. Furthermore, if measurements are to be used to distinguish the normal from the abnormal, regardless of the type of ballistocardiograph employed, it appears that rigid standardization of physiologic conditions will be essential for the most effective differentiation of the abnormal from the normal individual.

SUMMARY AND CONCLUSIONS

1. A ballistocardiograph was constructed that allowed high-frequency (Starr) ballistocardiograms and low-frequency, critically damped ballistocardiograms to be taken without moving the subject from the ballistocardiographic bed.

2. Ballistocardiograms were obtained on 51 young men, aged 18 to 26, and 57 middle-aged men, aged 50 to 59. Exercise, smoking, environmental temperature, and time after meals were controlled.

3. IJ amplitudes from both ballistocardiograms were most closely associated with height.

4. The correlation coefficients between IJ amplitudes and weight or surface area were lower when calculated with IJ amplitudes obtained with the high-frequency ballistocardiograph than those calculated with IJ amplitudes obtained with the low-frequency, critically damped apparatus. This was true of both age groups, but only in the younger group were the differences statistically significant.

5. The IJ amplitude between the two age groups decreased by 29 per cent when obtained with the high-frequency ballistocardiograph and 35 per cent as measured by the low-frequency, critically damped apparatus. When these

decrements were tested against the standard deviations of the young (reference group), it was shown that the low-frequency critically damped apparatus was more sensitive to the effects of age.

6. The application of these findings to the study of the epidemiology of coronary heart disease and to differentiating patients from normals is discussed.

It is a pleasure to acknowledge the cooperation of Mr. Walter Carlson, Junior Scientist, Mrs. Nedra Foster, Administrative Technologist, and Mr. Norris Schultz, Statistician, whose meticulous attention to detail and willing assistance were invaluable.

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INITIAL ELECTROCARDIOGRAPHIC CHANGES IN EXPERIMENTAL OCCLUSION OF THE CORONARY ARTERY IN NON-ANESTHETIZED DOGS WITH CLOSED THORAX

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RECENT articles on the electrocardiographic changes in the first stages of a myocardial infarction[1,2,20] show, in certain human cases, that the elevation of the T wave occurs before the inversion of the same wave. A revision of the experimental work already done shows that the presence of a high and peaked T wave has already been described, without there being present a current of injury[3]; as it has been pointed out by Smith,[4-6] this change comes before the changes of the RS-T segment. The changes described by Bayley and associates[7-9] in the terminal phase of the ventricular complex, have been corroborated by some recent articles[10,11]; however, if one carefully analyzes Smith's recordings, an associated current of injury will be found. The important findings of Bayley and associates showing increased voltage of the T wave without RS-T segment's shifting, as the first sign of coronary occlusion, were done in animals with open thorax and sometimes under the action of theophylline.

The present work tries to demonstrate the T-wave changes, putting aside all factors which could possibly interfere with the experiment, and so influence such changes.

MATERIAL AND METHOD

Five dogs were operated upon according to Allen and Laadt's technique,[12] with some changes devised by us. The animals were anesthetized with Pentothal sodium; the thorax and pericardium were opened and a loose knot was tied around the descending branch of the left coronary artery, previously isolated. The thread's ends were transfixed through anterior and posterior thoracic walls and firmly secured to the skin. Electrocardiographic recordings were taken before, during, and after these preparations. Several days later, once the operatory wound healed and the dogs completely recovered, a superficial anesthesia was induced with ether, an intratracheal tube was put in place, and a certain quantity (5 to 10 c.c.) of curare injected. After a few minutes, while the dogs were still awake though completely immobilized through the curare action, under artificial respiration the threads previously fixed to the skin were slowly pulled,

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while an electrocardiographic tracing was being continuously taken in V_3. Since the threads were of quite elastic nature, the same procedure could be repeated two or three times in the same dog. The threads were so pulled as to cause a complete arterial occlusion in all experiments. Some dogs died within the first few hours and the others in the following days. The myocardial infarction thus induced was macroscopically evident in all five dogs.

RESULTS

With the first electrocardiographic alteration of the coronary constriction an intense bradycardia was noted in all dogs. In one case sinus arrest of four seconds' duration was recorded (Fig. 1). In all cases T-wave changes were immediately noted: increased voltage, sometimes in a striking way (Fig. 2), and a shape with decidedly ischemic character: peaked wave with symmetrical branches. A tendency for the T wave's basis to broaden was noted at the same time; the Q-T interval was the same, and no shifting of the J point was recorded.

After a short period of time, from seconds to several minutes, a shifting of the RS-T segment was noted. In some cases where a shifting of the RS-T segment already existed, it was difficult to observe such a sequence of happenings when the artery was constricted for the first time; however, after the second and the third constrictions all elements were present (Fig. 3). By loosening the knot and avoiding any pulling of the thread's ends, the whole procedure followed an inverse path, i.e., the RS-T segment's shifting disappeared and after that the T wave slowly assumed its original shape. In one case, after the first constriction, the originally notched T wave decreased its voltage, became diphasic (Fig. 2), and only after several seconds presented the ischemic character already described; in this particular case the T wave took on immediately an ischemic character as the second and third constrictions took place.

In all cases, after a few minutes, a slurred R wave could be noticed. The P wave had a tendency to increase its voltage. In another case, after the second constriction only, a downward shift of the P-R segment was noted. In all cases after those initial changes already described, the RS-T segment's shifting increased and the T wave was continuously decreased until it became diphasic.

DISCUSSION

In the experiences so far recorded by other observers, the experimental conditions failed to reproduce those usually found in human beings. The coronary artery was occluded with open thorax and pericardium. The electrocardiographic data thus recorded were transferred to human beings. Despite the fact, however, that there is a possibility of correlating those experimental findings to human cases, they do not reproduce what happens in human coronary occlusion. The Pentothal sodium anesthesia can cause a shift of the RS-T segment in 80 per cent of the cases.[13] Electrocardiographic changes have been recorded after the opening of both thorax and pericardium.[14] The presence of air inside the thoracic cage induced some electrocardiographic changes, and the same can be said about the mediastinal shift and changes of the heart's position.[15] The

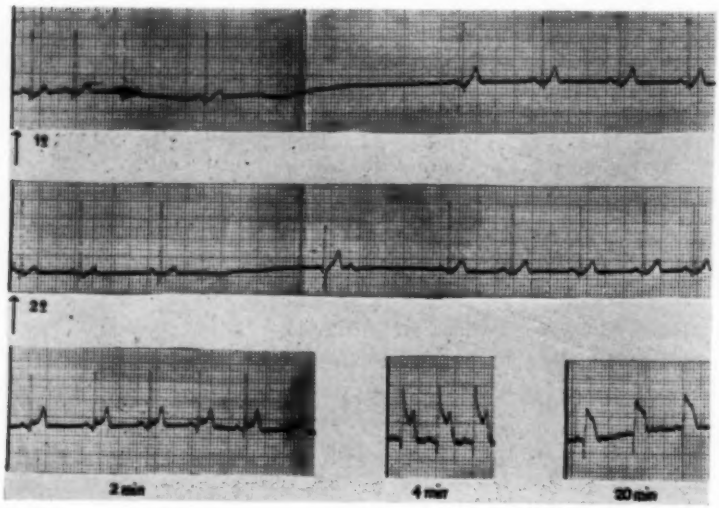

Fig. 1.

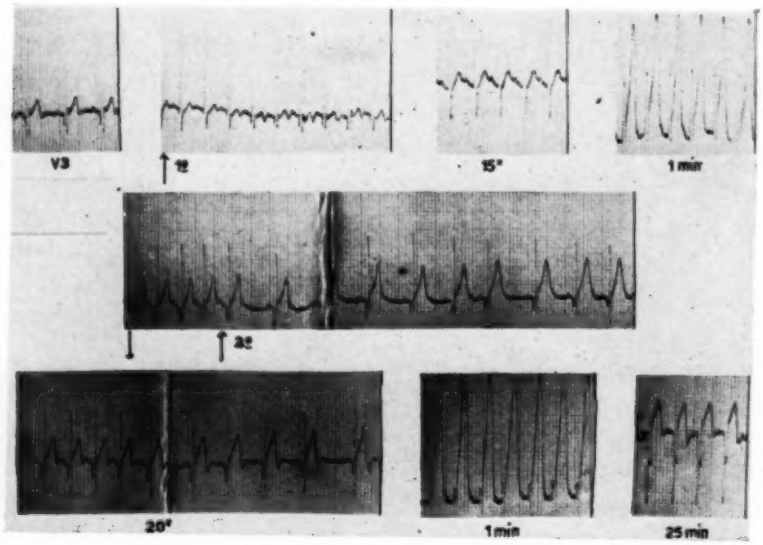

Fig. 2.

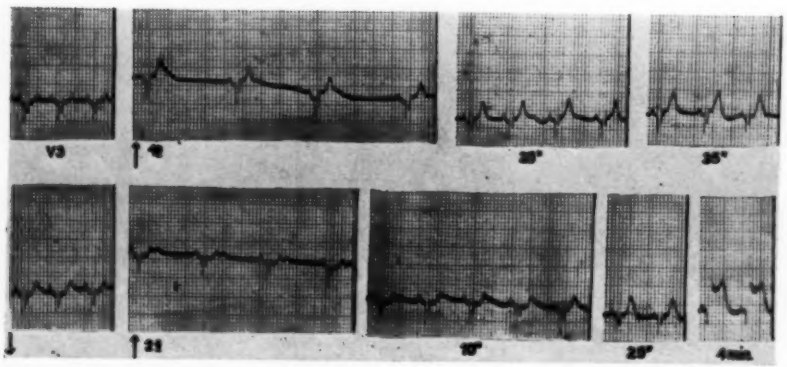

Fig. 3.

Figs. 1 to 3.—The constriction of the thread is marked with arrow pointing up. The loosening of the thread is marked with arrow pointing down.

close contact between heart and air can induce changes of the T-wave polarity, which is strongly affected by heat or cold as has been pointed out by Hellerstein and Liebow.[16] Besides, in the experimental work of Bayley and colleagues, the effect of the injected theophylline must be taken into consideration.

Our present method tries to overcome all those abnormal conditions, and thus resembles the human cases more closely. All changes which could be attributed to the opening of the thorax and pericardium, exposure of the heart to free air, were put aside. As to the curare action upon the heart, our own recordings failed to reveal any change which could be attributed to the drug. This point has been discussed already by other observers.[17] The only setback of our method is that we cannot take into consideration one very important factor in human cases: the pathologic conditions of the walls of the coronary arteries.

As has been already stated, the precordial leads were used, as is usually done in human cases.

From our observations, we have found that the first change to be noted in the T wave, after the occlusion, is the increased voltage and the alteration of the shape to an ischemic character. Only after this will appear polarity changes, current of injury, and changes of the initial ventricular complex.

The early increased voltage of the T wave might be interpreted as: (1) early reactive hyperemic state,[18] (2) closeness to ischemic areas of the infarcted zone, (3) predominance of subendocardial ischemia.[19] In the light of the last hypothesis, it has been observed that the RS-T segment changes the direction of its shifting from a negative to a positive, shortly after the coronary artery has been occluded.[15]

CONCLUSION

The gradual occlusion of the descending branch of the left coronary artery in nonanesthetized dogs and with closed thorax resulted in an increase of the positive T-wave voltage, together with its change toward the ischemic shape. After those early changes, others followed, as partial inversion of the T wave, displacement of the RS-T segment, changes of the QRS complex, etc.

SUMMARY

The authors devised a method that allows the gradual occlusion of the descending branch of the left coronary artery of nonanesthetized dogs with closed thorax. These experimental conditions try to reproduce what happens in human beings. A continuous electrocardiographic recording in V_3 disclosed that the first sign of a coronary occlusion is an increase of the T-wave voltage. Changes of the rhythm, the QRS complex, and of the auricular complex were also seen. These T-wave changes are quite similar to those recently described in the very early stages of a human myocardial infarction.

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ON THE DISTRIBUTION OF CORONARY THROMBOSIS ATTACKS

A Statistical Analysis of 396 Cases

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DURING the last thirty years several papers considered the effect of weather conditions on the occurrence of cases of myocardial infarction. Generally speaking, the views are controversial. Some writers[1-10] suggest that cold weather, others[11] suggest that hot weather increases the incidence of attacks. The latter writers[12] now favor the opinion that the sudden influx either of polar or of tropical air masses augments the number of cases. A third group of writers[13-16] represents the view that there is no significant meteorological influence that can be discerned in the distribution of cases.

In a recent investigation one of us (Z.L.) examined the matter on the basis of the material from cases hospitalized at the Beilinson Hospital. The results did not indicate any significant seasonal variation in the incidence of attacks, except for October, which in the monthly breakdown of cases showed consistently lower figures, whose mean differed significantly from the mean of the remaining months. The significance of this could not be established and no correlation could be found between the occurrence of the attack of myocardial infarction and any of the known and measurable meteorological characteristics such as maxima or minima of temperatures, relative humidity, wind strength, or amount of rain.

We have now re-examined the data.

MATERIAL AND METHOD

In the period of Jan. 1, 1949, to June 30, 1953, a total of 1,618 cases of first and recurrent myocardial infarctions were diagnosed among the members of the Sick Fund of Jewish Labour in Israel (Kupat Holim). Of these, 396 with an electrocardiographically, clinically, or pathologically proved diagnosis were hospitalized at the Beilinson Hospital (24 per cent) and serve as the material for this report.

The Beilinson Hospital, which belongs to the Sick Fund, is situated in an area with a population of more than 500,000, about 60 per cent of whom are members of the Sick Fund. Because of scarcity of data on the rest of the population, it could not be established in a quantitative fashion if the sample studied

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is a completely random one. However, as the population* from which this sample is drawn represents about 60 per cent of the whole population and the membership of the Labour Sick Fund includes, in addition to industrial and agricultural workers, intellectual workers, clerks, and a proportion of shopkeepers it is not too small a one. In view of these facts it is probably reasonable to assume that the sample studied is a random sample. Only cases where the day of the attack could be established were included in the analyses.

The incidence of attacks was broken down in a dichotomic fashion, in a cold and warm season, and the days were added and tabulated according to the number of attacks which had occurred in them.

RESULTS

The distribution of the number of attacks per day and season is stated in Table I.

TABLE I. NUMBER OF ATTACKS OF CORONARY THROMBOSIS PER DAY AND NUMBER OF DAYS IN A PERIOD COMPRISING FOUR AND ONE-HALF YEARS

NUMBER OF ATTACKS PER DAY	COLD SEASON, OCTOBER TO MARCH	WARM SEASON, APRIL TO SEPTEMBER	PER YEAR
0	631	615	1246
1	162	174	336
2	23	31	54
3	3	3	6
4	0	0	0
Totals	819	823	1642

Since the incidence of myocardial infarction is very small relative to the size of the population, it is natural to conjecture that the incidence of attacks follows a Poisson distribution. In a Poisson distribution, the mean μ equals the variance σ^2, or $\mu = \sigma^2$. Now, it is readily found from Table I that:

> No attacks occurred in 1,246 days of the examined period, 1 attack per day occurred in 336 days, 2 in fifty-four, and 3 in six days of the period. There was no day in the whole period where 4 or more attacks occurred.

The calculated means and variances from Table 1 are:

	(*Mean*) μ	(*Variance*) σ^2
Cold Season	0.265	0.273
Warm Season	0.298	0.306
Year	0.281	0.290

The closeness of the respective means and variances supports, indeed, the conjecture that the cases are distributed according to Poisson's method. In a Poisson distribution whose mean is μ, the probability $\pi\ (n;\mu)$ of n cases occurring is

$$\pi\ (n;\mu) = \frac{\mu^n}{n!}\, e^{-\mu},\ n = 0, 1, 2, \quad \ldots$$

*Here the term "population" has its common and not its statistical meaning.

Introducing into the equation the values of μ as listed above and multiplying the probabilities into the appropriate number of days (N) set down in Table I, we arrive at Table II.

TABLE II. NUMBER OF ATTACKS OF CORONARY THROMBOSIS PER DAY CALCULATED FROM POISSON DISTRIBUTIONS

NUMBER OF ATTACKS PER DAY (n)	COLD SEASON		WARM SEASON		YEAR	
	P	F	P	F	P	F
0	0.767	628.2	0.742	610.7	0.755	1239.8
1	0.203	166.2	0.221	181.9	0.212	348.1
2	0.027	22.1	0.033	27.2	0.0297	48.8
3	0.0024	2.0	0.003	2.5	0.0028	4.7
$\geqslant 4$	0.0006	0.5	0.001	0.8	0.0005	0.8
Totals		819.0		823.1		1642.2

P = probability = π (n;μ); F = Frequency = N.π (n;μ); N = number of days in respective periods.

A comparison between the calculated frequencies (Table II) with the observed frequencies (Table I) will show that the accord is very satisfactory. Application of the χ^2 test gives a probability of over 0.50 that in each case the differences between the theoretical and observed frequencies could have arisen solely due to chance.

There remains the question of whether the difference in the seasonal means indicate a genuine seasonal variation in the incidence of attacks. Let us test the hypothesis that the data for the cold and warm seasons were taken from the same population (see footnote, page 340) and that the mean for the population is 0.281, i.e., the mean for the combined winter-summer sample. Now, the sampling error of the mean is $\sigma/\sqrt{N}$, = N being the number of members in the sample. It is readily calculated that the sampling error of the means for both the cold and warm seasons is 0.018 (very nearly), so that the seasonal means differ by less than one standard error from the hypothetical population mean. Thus, we have no reason to reject the hypothesis that there is no seasonal variation indicated by the data.

DISCUSSION AND CONCLUSIONS

The conclusions which can be drawn from the above simple analysis appear to go deeper than the mere question of seasonal variation as well as beyond the local significance of the results.

Theoretically, the Poisson distributions represent the distributions of random variables which take on mutually independent values. The good agreement shown by the observed numbers of attacks and the numbers calculated from the Poisson distributions suggests that the attacks of myocardial infarction are distributed in a random fashion and that the attacks occur independently from each other. This is one more reason why we are dubious if weather conditions influence the incidence of attacks.

The medical and meteorological literature abounds in papers trying to establish causal relationship between meteorological factors and incidence of several diseases. We feel that the random nature of the distribution of some diseases is worthy of consideration.

SUMMARY

A statistical analysis of the incidence of attacks of proved myocardial infarctions in patients hospitalized in Beilinson Hospital in the period January, 1948, till July, 1953, showed that these followed a Poisson distribution. This suggests that the incidence of myocardial infarction may be of a random nature rather than influenced by any weather condition.

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DIFFICULTIES IN INTERPRETATION OF RIGHT HEART CATHETERIZATION DATA

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ON OCCASION failure to realize the limitations of data obtained by cardiac venous catheterization has led to regrettable errors in diagnosis and management of heart disease. It is the purpose of this paper to describe eleven patients suffering from various forms of heart disease in whom data obtained by cardiac venous catheterization were either misleading or potentially so.

The cases to be reported comprise the following problems: tricuspid stenosis; constrictive pericarditis; pulmonary stenosis; differential diagnosis of shunts of oxygenated blood into the right atrium; differential diagnosis of aortic valve disease and patent ductus arteriosus; differential diagnosis of ventricular septal defect and patent ductus arteriosus; differential diagnosis of atrial septal defect and anomalous pulmonary venous drainage; anomalous pulmonary arteries; artefactual right atrial and coronary sinus pressures. In nine of the eleven cases to be described, the diagnosis was established by operation or autopsy. In some instances, the difficulty lay in technical errors in obtaining the catheterization data; in others, properly recorded data were misinterpreted or were not specific.

METHODS

The patients studied were fasting. Adults were sedated with 0.1 Gm. Nembutal; children were heavily sedated either with morphine 1 mg. per 4.5 kg. body weight and sodium phenobarbital 3 mg. per kilogram, or were anesthetized with rectal and intravenous Pentothal sodium. Cardiac venous catheterizations were performed as described by Cournand and Ranges.[1] Blood samples were analyzed for oxygen in the Van Slyke apparatus. Duplicates were required to check within 0.2 c.c. per 100 c.c. Intracardiac pressures were recorded with the Hathaway 5 channel optical oscillograph or with the Sanborn Poly-Viso direct writing electrocardiograph.

CASE 1.—*Rheumatic heart disease; mitral stenosis; possible tricuspid stenosis:* F. S., a 41-year-old white woman had had rheumatic heart disease with heart failure since 1940. In December, 1953, the patient was treated for tuberculous peritonitis and severe congestive heart failure. In April, 1954, upon her final hospital admission, she was found to have auricular fibril-

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lation, distended pulsating neck veins, and a greatly enlarged pulsating liver. There was but slight orthopnea. She had a Grade 2 apical systolic murmur which was somewhat louder at the tricuspid area. A faint soft apical diastolic murmur was heard. No tubercle bacilli were found in the ascitic fluid on this admission.

Cardiac catheterization revealed no evidence of a shunt. Arteriovenous oxygen difference was 8.2 c.c. per 100 cubic centimeters. Mean right atrial pressure was 18 mm. Hg. Right ventricular pressure was 66/12 mm. Hg.

A continuous record taken as the catheter tip was withdrawn from right ventricle to right atrium revealed that right atrial end-diastolic pressure was 8 mm. Hg higher than that in the right ventricle.

The patient expired the morning after an unsuccessful attempt at mitral commissurotomy. Autopsy revealed that the tricuspid valve ring was 12.5 cm. in diameter with thick rolled edges indicating tricuspid insufficiency. There was no evidence of tricuspid stenosis. The mitral valve orifice was 2.5 by 2 mm. indicating severe stenosis. Its leaflets were fused. The other cardiac valves were normal.

Comment: In this patient, the persistent pulsations of the liver and neck veins, recurrent ascites, and relative absence of orthopnea strongly suggested tricuspid valve insufficiency. The pattern of tricuspid insufficiency was found in the right atrial pressure pulse tracing. This was considered to be of little help, since this pattern is observed in the majority of patients with mitral stenosis and auricular fibrillation, according to Ferrer and co-workers.[2] In the present instance, the differences in right atrial and right ventricular end-diastolic pressures of 8 mm. suggested additional tricuspid stenosis, since Ferrer and co-workers[3] reported no difference between these pressures exceeding 2 mm. Hg with tricuspid insufficiency in the absence of tricuspid stenosis, regardless of the height of the diastolic pressure. In spite of the pressure difference observed in our patient, only tricuspid insufficiency and mitral stenosis were found at autopsy.

CASE 2.—*Possible constrictive pericarditis:* F. S., a 51-year-old white patrolman became ill with dyspnea three years prior to admission. Two and one-half years prior to admission, he had developed dependent edema. There was a past history of alcoholism. On examination, he was found to have ascites, distended neck veins, and an apical mid-diastolic gallop rhythm. The only cardiac murmur was a soft blowing apical systolic murmur. The liver was enlarged four fingerbreadths below the right costal margin. An electrocardiogram revealed auricular fibrillation, a ventricular conduction defect, and questionable evidence of healed anterior myocardial infarction.

Cardiac venous catheterization revealed no evidence of a shunt. Pressures in millimeters of mercury were: right atrium, 18; right ventricle 48/19; pulmonary artery 56/30; pulmonary wedge, 28. Arteriovenous oxygen difference was 6.6 c.c. per 100 c.c.

The patient continued to have severe congestive heart failure, and died four months later. Autopsy revealed normal pericardium and heart valves. The myocardium showed widespread edema, with atrophy and interstitial fibrosis. There was minimal coronary sclerosis. No nerve section was obtained. The findings were considered consistent with beriberi heart disease, although idiopathic myocarditis was also a possibility.

Comment: During life, this patient was believed to have myocardial disease, probably due to coronary sclerosis, as the cause of his heart failure. However, persistent elevation in venous pressure and relatively slight orthopnea led to a consideration of constrictive pericarditis as a possibility. The right ventricular pressure was 48/19, measured by cardiac catheterization. It has been suggested[4] that constrictive pericarditis is to be suspected when the right

ventricular diastolic pressure exceeds one-third of the systolic pressure. According to this criterion, the high right ventricular diastolic pressure of this patient would have been suggestive of cardiac constriction. However, the pronounced diastolic dip described by Hansen and co-workers[5] was not present here. In addition, narrow right ventricular pulse pressure may be seen in subendocardial fibroelastosis, in amyloid disease of the heart, and in diffuse myocardial fibrosis.[6,7] Further, the "plateau" described by Sawyer and associates[8] was absent here; although the systemic venous and right atrial mean and right ventricular diastolic pressures were equal, there was a considerable rise from these values to the pulmonary arterial diastolic and pulmonary "wedge" pressures. For this reason, exploratory thoracotomy was not undertaken in the present case.

CASE 3.—*Congenital heart disease; possible pulmonic stenosis:* J. M., a 12-year-old girl, was admitted for study because of episodes of dyspnea, cyanosis, and tachycardia on exertion or excitement for a period of one year.

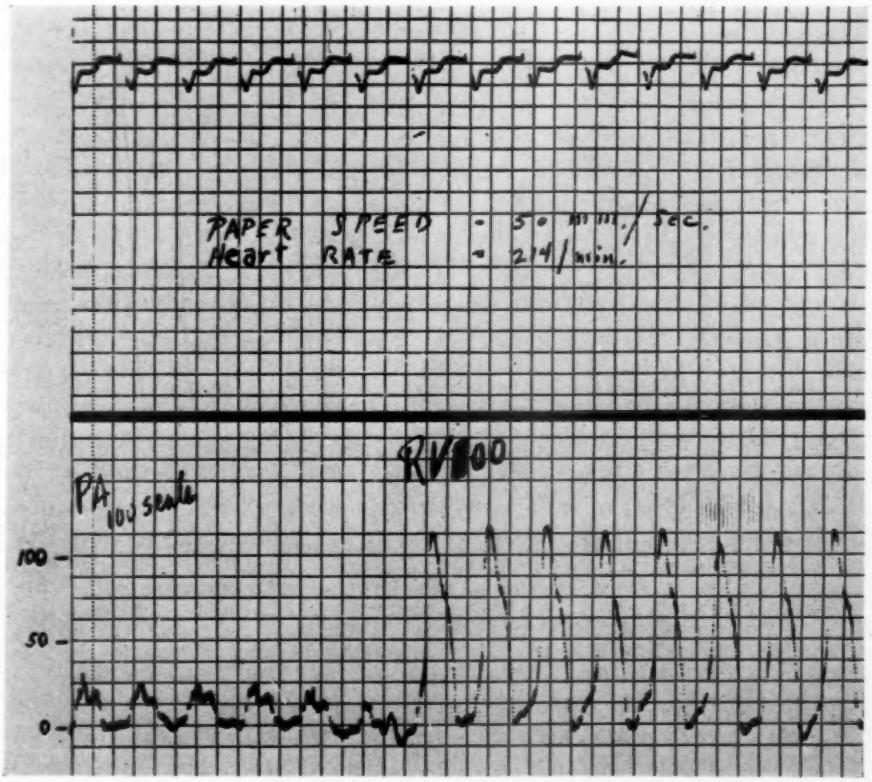

Fig. 1.—Case 3. Continuous pressure record taken as catheter tip was drawn from pulmonary artery to right ventricle, during paroxysmal tachycardia. Pulmonary arterial pressure is recorded at 24/1 mm. Hg; right ventricular pressure is 112/9 mm. Hg. The record simulates pulmonary stenosis, which was not present at operation. The patient had pulmonary hypertension, probably associated with a ventricular septal defect.

Physical examination revealed a Grade 4 systolic murmur at the pulmonic area, and along the left sternal border. The pulmonary second sound was diminished. There was no cyanosis; the lungs were clear, and the liver not enlarged.

An electrocardiogram showed right ventricular hypertrophy.

Chest x-rays showed marked right ventricular enlargement. The pulmonary vascular markings were normal to increased. The main pulmonary artery was prominent.

Right heart catheterization was done. When the catheter tip entered the pulmonary artery, the patient developed paroxysmal tachycardia, with a ventricular rate of 240 per minute (Fig. 1). Before withdrawing the catheter, pulmonary arterial pressure was recorded as 24 per 1 mm. Hg and right ventricular pressure as 112/8 mm. Hg (Fig. 1). Systemic arterial oxygen saturation was 84 per cent of capacity. Because of the paroxysmal tachycardia, blood samples from the right heart chambers were not taken.

The clinical diagnosis was pulmonic stenosis, and this was believed confirmed by the large systolic pressure gradient between right ventricle and pulmonary artery.

A thoracotomy was done (by E.P.M., Jr.). A 15 mm. urethral sound was easily passed through the right ventricular outflow tract and into the pulmonary artery without obstruction. A thrill over the entire surface of the right ventricle characteristic of ventricular septal defect was found. Pressures were recorded during the operation from right ventricle and pulmonary artery, using a needle and Statham strain gauge. No systolic pressure gradient between pulmonary artery and right ventricle was observed.

Comment: The catheter tip during recording of the pulmonary arterial pressure was definitely outside the right ventricle. The low pulmonary arterial pressure recorded in this patient was artefactual possibly because of obstruction of the catheter tip by abutting against the wall of the vessel. This experience emphasizes the desirability of confirming right ventricular-pulmonary arterial pressure gradients by repeating the passage of the catheter through the pulmonary valve area and of confirming the patency of the catheter by passing fluid through it when such a pressure difference is recorded.

In addition to this type of error in the diagnosis of pulmonary stenosis, Rudolph and co-workers[9] have recently pointed out that relative pulmonary stenosis due to large left-to-right shunts may produce considerably higher right ventricular than pulmonary arterial systolic pressures. Further, artefactual differences in pulmonary arterial and right ventricular systolic pressures may be observed. In simultaneously recorded right ventricular and pulmonary arterial pressure curves of the normal dog, using cardiac catheters, we have observed right ventricular systolic pressures as much as 14 mm. Hg higher than those in the pulmonary artery in the absence of obstruction at the pulmonary valve.

CASE 4.—*Anomalous pulmonary artery resembling patent ductus arteriosus:* J. W.,* a 15-year-old white girl, was seen because of a continuous murmur heard maximally over both infrascapular areas posteriorly and heard with less intensity anteriorly in the third right intercostal space. Systemic pulse pressure was increased. There was no cyanosis.

Both chest x-ray and electrocardiogram revealed left ventricular hypertrophy.

Cardiac catheterization showed an increase in oxygenation of pulmonary arterial blood of 1.1 vol. per cent on the right, and of 3.5 vol. per cent on the left. Right heart and pulmonary arterial pressures were normal. Fig. 2, an angiocardiogram, shows filling of an anomalous pulmonary artery from the abdominal aorta. At thoracotomy, the diameter of the anomalous artery was slightly in excess of 1 cm. The right lower lobe was resected. The anomalous artery was shown on injection to break up into multiple small channels which communicated with the pulmonary arteries. Following operation, the continuous murmur disappeared.

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*The authors wish to thank Dr. Sterling Claiborne, of Atlanta, for permission to report this patient. This case is being reported in detail elsewhere.

Comment: The cardiac catheterization of this patient showed evidence of a shunt from a systemic artery, presumably aorta, into the pulmonary artery. The commonest cause of such a shunt is persistent patency of the ductus arteriosus. However, the much greater increase in right than in left pulmonary artery oxygenation would be unusual in patent ductus arteriosus. The distribution of the murmur in this patient, being maximal over the right lower posterior thorax, clearly indicated that some other type of arteriovenous fistula was to be strongly considered. Such was found to be the case. The matter of anomalous pulmonary arteries arising from the aorta has been reviewed by Mannix and Haight.[10]

Fig. 2.—Case 4. Angiocardiogram seven seconds after dye injection. Arrow indicates anomalous pulmonary artery arising from abdominal aorta. Note multiple small anastomotic channels in right lower lobe and filling of large pulmonary veins draining this area.

CASE 5.—*Congenital heart disease; left-to-right shunt into the right atrium:* A. W., a 29-year-old white housewife, was seen because of a history of a cardiac murmur since the age of 12.

There was no historical or physical evidence of heart failure. There was no tachycardia, cyanosis, clubbing, or widening of the pulse pressure. There was a continuous murmur, loudest in the fourth left intercostal space adjacent to the sternum. Electrocardiogram was normal. Chest fluoroscopy revealed increased pulsations of the pulmonary artery. The heart was thought not to be enlarged.

Cardiac venous catheterization revealed the data in Table I.

An exploratory thoracotomy was performed June 7, 1954 (by E.P.M., Jr.). A continuous thrill was felt over the lower right atrium. The right atrium was opened, and a communication with the left ventricle was found. The heart and chest were closed without attempting to repair the defect.

TABLE I

	O_2 CONTENT (C.C./100 C.C.)	PRESSURES (MM. HG)
SVC*	11.5	—
IVC	13.9	—
RA (high)	11.4	3.0
(low)	14.1	—
RV	14.5	21/3
PA	14.3	19/8 (12, mean)
BA	16.8 (100% sat.)	—
Pulmonary wedge	—	7.0

*The following abbreviations are used in this paper:

SVC-Superior Vena Cava.
IVC-Inferior Vena Cava.
RA-Right Atrium.
RV-Right Ventricle.
PA-Pulmonary Artery.
FA-Femoral Artery.
BA-Brachial Artery.
LA-Left Atrium.

Comment: If the blood gas data were interpreted without regard for the clinical picture, an interpretation of atrial septal defect or anomalous pulmonary venous drainage into the lower right atrium might be made. The presence of a continuous murmur in this case, however, suggested a communication between the right atrium and the systemic circulation. The preoperative diagnosis in this case was that of a fistula between an aortic sinus of Valsalva and the right atrium.

CASE 6.—*Possible patent ductus arteriosus:* N. B., a 28-year-old Negro woman, was admitted Sept. 29, 1954. There was a questionable history of rheumatic fever at the age of 10. For six months she had had dyspnea, orthopnea, and dependent edema.

Examination revealed apical systolic and diastolic thrills and murmurs. Grade 2 systolic and diastolic murmurs were heard at the base of the heart, loudest in the aortic area. Blood pressure was 138/48 mm. Hg. Neck veins were distended, and the liver edge was felt four fingerbreadths below the right costal margin. Venous pressure was 170 mm. of water, and decholin circulation time was 32 seconds. An electrocardiogram revealed left axis deviation and left ventricular hypertrophy. Chest x-ray revealed left ventricular enlargement and prominence of the pulmonary arterial segment.

Clinical opinion was divided between a diagnosis of patent ductus arteriosus and that of rheumatic heart disease involving mitral stenosis and insufficiency, and aortic stenosis and insufficiency.

Cardiac venous catheterization was done Oct. 8, 1954. The results are shown in Table II.

TABLE II

	O_2 CONTENT (C.C./100 C.C.)	PRESSURES (MM. HG)
SVC	9.9	—
RA	8.6	11
	8.3	—
RV	8.7	60-70/10-11
	8.2	
PA	9.4	60-70/35-38
	9.1	
	9.6	
BA	13.4 (92% sat.)	132/60

These data were interpreted as indicating pulmonary hypertension and a shunt of oxygenated blood into the pulmonary artery, consistent with patent ductus arteriosus.

Thoracotomy was performed Oct. 28, 1954 (by E.P.M., Jr.). Patent ductus arteriosus was not found. Systolic and diastolic thrills were felt maximally over the aortic valve. It was believed that the patient had aortic stenosis and insufficiency. Cardiac catheterization was repeated postoperatively. No evidence of left-to-right shunt was found.

Comment: This case illustrates the difficulty in interpreting small increases in oxygenation of pulmonary arterial blood. Whether this variation was due to failure to maintain a steady state, or streamline flow of more highly oxygenated blood from the superior vena cava, cannot be said with certainty. The wide systemic arterial pulse pressure demonstrated by this patient indicated that evidence suggesting a larger shunt would be expected if this wide pulse pressure were due to a patent ductus arteriosus. Certainly, some patients with patent ductus arteriosus will have no greater evidence of arterialization of pulmonary arterial blood than that suggested here.

CASE 7.—*Congenital heart disease; possible patent ductus arteriosus:* J. E., a 12-year-old Puerto Rican boy, was admitted to the hospital for evaluation Dec. 17, 1953.

Physical examination revealed blood pressure of 100/70 mm. Hg and weight of 59 pounds. The child was poorly nourished and developed. There was no cyanosis or clubbing. The heart revealed a harsh systolic murmur and a thrill maximal in the second left intercostal space adjacent to the sternum. The pulmonary second sound was equal to the aortic second sound in intensity. X-rays revealed slight enlargement of the heart with prominence of the pulmonary artery. Electrocardiogram was normal; the electrical axis was normal.

Cardiac catheterization was done on Dec. 29, 1953. Table III gives the results.

TABLE III

	O_2 CONTENT (C.C./100 C.C.)	PRESSURES (MM. HG)
Pulmonary vein	16.7	—
SVC	11.6	—
RA (high)	13.8	11
RA (near pulmonary vein)	15.4	—
RV (high)	13.3	45/9
RV (low)	13.5	
PA	14.5; 14.6	44/18
BA	16.8 (100% sat.)	144/88

The cardiac catheter entered an anomalous pulmonary vein draining into the right atrium.

The increase in oxygenation of pulmonary arterial over right ventricular blood of 1.1 vol./100 c.c. was considered suggestive of patent ductus arteriosus. Exploratory thoracotomy was done on Jan. 13, 1954 (by E.P.M., Jr.). The ductus arteriosus was isolated and divided, and was shown to be obliterated. The pericardial cavity was opened. A thrill was felt over the pulmonary artery. No definite evidence of pulmonary stenosis could be found. A high ventricular septal defect was believed to be present.

Comment: The apparent oxygenation of the pulmonary arterial blood is believed due to a left-to-right shunt through a high ventricular septal defect in this instance. The absence of a diastolic component of the pulmonary murmur in the presence of only mild pulmonary hypertension, should militate against the diagnosis of patent ductus arteriosus. Damman and Sell[11] have shown the

difficulty in distinguishing between shunts of oxygenated blood into the upper right ventricle through a ventricular septal defect and those into the pulmonary artery through a patent ductus arteriosus or aortic septal defect. This difficulty may occur even when right ventricular samples are taken just below the pulmonary valve, as shown in the report of Case 9.

Another situation which may give rise to an incorrect diagnosis of patent ductus arteriosus is the contamination of the pulmonary arterial blood samples by pulmonary venous blood. This may occur when the catheter tip is placed too far peripherally in the pulmonary artery so that a wedging effect is obtained. On occasion, the catheter may be forced into this position by the blood stream, even though placed in the proper position originally.

CASE 8.—*Congenital heart disease; ventricular septal defect versus patent ductus arteriosus:* V. M., a 6-year-old boy, was referred for study of congenital heart disease. Examination revealed no cyanosis or clubbing, and normal femoral pulsations. Systemic blood pressure was 95/42 mm. Hg. There was a precordial systolic murmur, maximal in the pulmonary valve area, followed by a diastolic murmur of a faint humming quality.

Cardiac venous catheterization was done on Jan. 5, 1954. The results are shown in Table IV.

TABLE IV

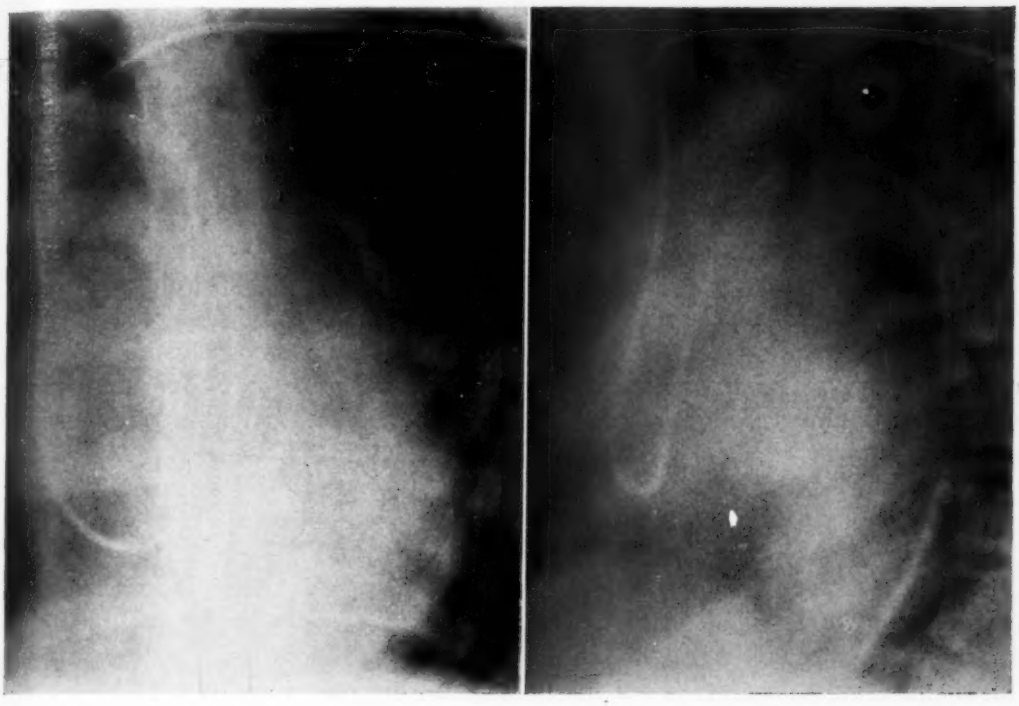
	O_2 CONTENT (C.C./100 C.C.)	PRESSURES (MM. HG)
RA	12.0	—
RV (inflow)	11.7	—
RV (outflow)	13.2	—
PA	14.0; 14.0	32/19 (mean 25)
BA	17.3 (93% sat.)	95/42

A thoracotomy was performed subsequently (by E.P.M., Jr.). A patent ductus arteriosus 8.5 mm. in external diameter was found and ligated. Following this procedure, no cardiac murmurs were heard.

Comment: Interpretation of the blood gas data in this instance, without regard for the clinical picture, might easily lead to error. There is greater increase in oxygenation of the high right ventricular sample than there is further increase in oxygenation of the pulmonary arterial samples. This is presumably due to pulmonary regurgitation complicating patent ductus arteriosus.[12] From the blood gas data alone, an interpretation of ventricular septal defect might easily be made. However, the presence of a diastolic murmur in the pulmonary valve area, in the absence of sufficient pulmonary hypertension or pulmonary flow to produce a Graham Steell murmur, seemed to make ventricular septal defect alone unlikely. The disappearance of all murmurs postoperatively made it unlikely that this patient had both ventricular septal defect and patent ductus arteriosus.

CASE 9.—*Congenital heart disease; possible patent ductus arteriosus versus ventricular septal defect:* R. J., a 15-year-old white girl, was admitted for study on April 13, 1955. She had a lifelong history of weakness and case of fatigue, along with a cardiac murmur and poor development. A cardiac catheterization had been performed March 25, 1954.

Physical examination revealed no cyanosis, clubbing, or obvious distress. Blood pressure was 100/70 mm. Hg. There were dorsal kyphosis and diminution in stature. There was Grade



A. *B.*

Fig. 3.—Case 9. Posteroanterior (*A*) and left anterior oblique (*B*) x-ray films of ventricular septal defect, showing cardiac catheter entering aorta from right ventricle.

2 systolic murmur in the third left intercostal space adjacent to the sternum. The pulmonci second sound was accentuated. There were an apical presystolic and mid-diastolic rumbling murmur. Femoral pulses were normal.

An electrocardiogram was suggestive of left ventricular hypertrophy. X-ray and fluoroscopy of the chest revealed prominence of pulmonary arteries and enlargement of the left ventricle without increased pulsation of the pulmonary vessels.

Cardiac catheterization was repeated April 14, 1955. A comparison of the data obtained during the first and second catheterizations is given in Table V.

TABLE V

	O_2 CONTENT C.C./100 C.C.	O_2 CONTENT (C.C./100 C.C.) % SATURATION	PRESSURES (MM. HG)	
	FIRST	SECOND	FIRST	SECOND
SVC	9.9	10.5 (62%)	—	—
IVC	—	8.9 (52%)	—	—
RA (high)	8.1, 7.9	10.2 (60%)	—	—
RA (mid)	8.1, 7.9	9.4 (55%)	2/0	3.0 (mean)
RA (low)	—	8.8 (51%)	—	—
RV	7.9, 8.4	9.7 (57%)	55/36 (damped)	110/2
RV (outflow tract)		10.7 (63%); 12.6 (74%)	—	—
PA (main)	12.5	12.6 (74%); 15.2 (90%)	73/65 (damped)	104/67
PA (rt)	13.1	14.5 (86%)	—	—
FA	—	16.6 (97%)	—	116/60
Aorta	—	15.9 (94%)	—	112/73

After the first cardiac catheterization, the large increase in oxygenation of pulmonary arterial over right ventricular blood was interpreted as evidence of patent ductus arteriosus with associated pulmonary hypertension.

During the second study, the catheter was passed into the aorta from the right ventricle. The course of the catheter is shown in Figs. 3,*A* and *B*. The direction taken by the catheter here seems to exclude the possibility of patent ductus arteriosus alone, in which instance the catheter would be expected to pass farther to the left and anteriorly before entering the aorta.

Comments: At the first study, the lowering of systolic pressure peak levels by damping obscured the fact that systolic pressures in the pulmonary and systemic circulations were virtually identical; thus the possibility of overriding aorta was unjustifiably eliminated. The very high diastolic pressure obtained from the damped right ventricular pressure curve were factitious since right ventricular filling could not occur with the much lower right atrial pressure which existed.

Second, this case illustrates again the difficulty in detecting shunts of oxygenated blood into the right ventricle through a ventricular septal defect. Only one of five ventricular samples obtained in the two studies showed evidence of the shunt. Even with this information, the further increase in oxygenation of pulmonary arterial blood of 2.6 vol. per 100 c.c. would render it difficult to eliminate the possibility of patent ductus arteriosus alone with pulmonary insufficiency being responsible for the increase in oxygenation observed in the one right ventricular sample.

Even with complete information regarding pressure curves and blood gas data in this patient, the diagnosis of ventricular septal defect could not have been made with certainty without passing the catheter directly into the aorta. The combination of high ventricular septal defect with probable overriding of the aorta on the one hand and patent ductus arteriosus on the other is a possibility.

CASE 10.—*Congenital heart disease; anomalous pulmonary venous drainage versus atrial septal defect:* This 15-year-old underdeveloped Negro boy had a negative history and was acyanotic. The heart revealed an accentuation of the pulmonic second sound and a Grade 3 systolic murmur maximal in the third left intercostal space. Cardiac fluoroscopy revealed right ventricular enlargement and prominent pulsating pulmonary arteries. The electrocardiogram showed incomplete right bundle branch block. A clinical diagnosis of atrial septal defect was made and cardiac venous catheterization was performed June 7, 1955. The results are shown in Table VI.

TABLE VI

	OXYGEN CONTENT (C.C./100 C.C.)	PER CENT SATURATION	PRESSURES (MM. HG)
SVC	6.6	60	—
IVC	7.3	66	—
RA (high)	6.5	59	3
RA (low)	8.2	75	—
RV (inflow)	8.6	79	50/3
(outflow)	8.6	79	—
PA	8.8	80	41/5
	8.5	78	
Rt. (pulmonary vein)	9.6	87	6
LA	9.1	83	5
FA	9.9	90	—

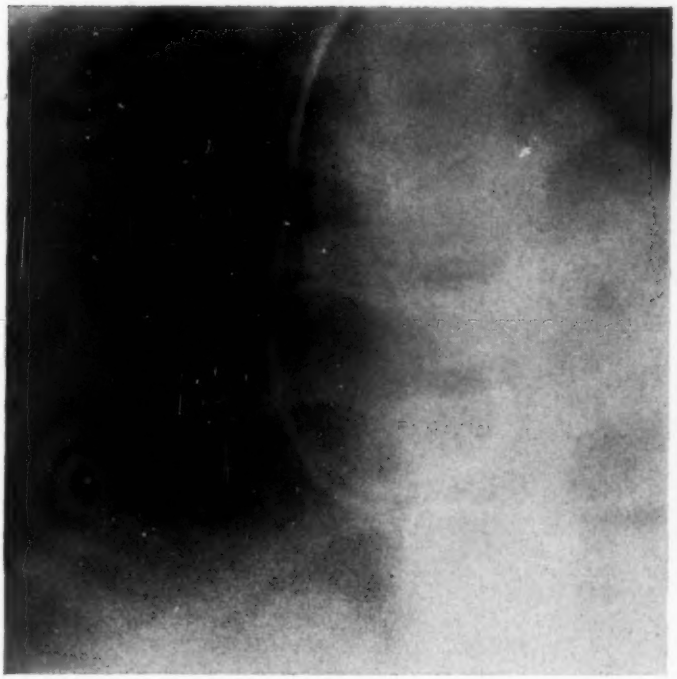


Fig. 4.—Case 10. Atrial septal defect. X-ray showing catheter tip in a right pulmonary vein, apparently entering this vein from the right atrium. (See Fig. 6.)

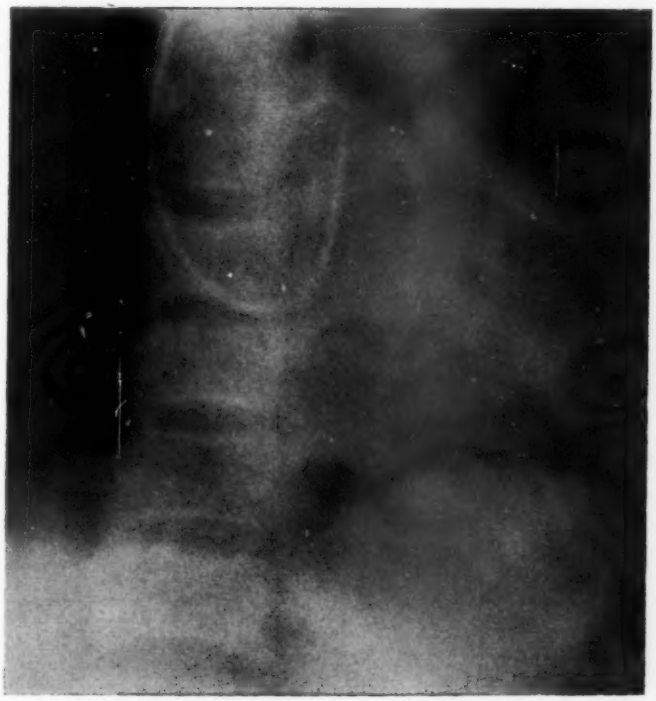


Fig. 5.—Case 10. X-ray showing catheter tip lying in left atrium, having assumed this position upon withdrawal from position shown in Fig. 6. Catheter tip has passed through an atrial septal defect.

The cardiac catheter tip was passed from the cardiac shadow into the right lung field. The low pressure here (mean = 6 mm. Hg) and the high oxygen saturation of the blood, although somewhat low for pulmonary venous blood, indicated that the catheter tip lay in a pulmonary vein. The fluoroscopic and x-ray appearance (Fig. 4) suggested that there was an anomalous pulmonary vein draining into the right atrium. However, the course taken by the catheter tip upon withdrawal (Fig. 5), together with the degree of oxygenation of the blood samples taken as the catheter was withdrawn, suggested that the catheter had passed from right to left atrium through an atrial septal defect, and had then entered the right pulmonary vein from the left atrium. On Sept. 5, 1955, a thoracotomy was performed. An atrial septal defect, 3 cm. in diameter, of the persistent ostium secundum type, was found and repaired.

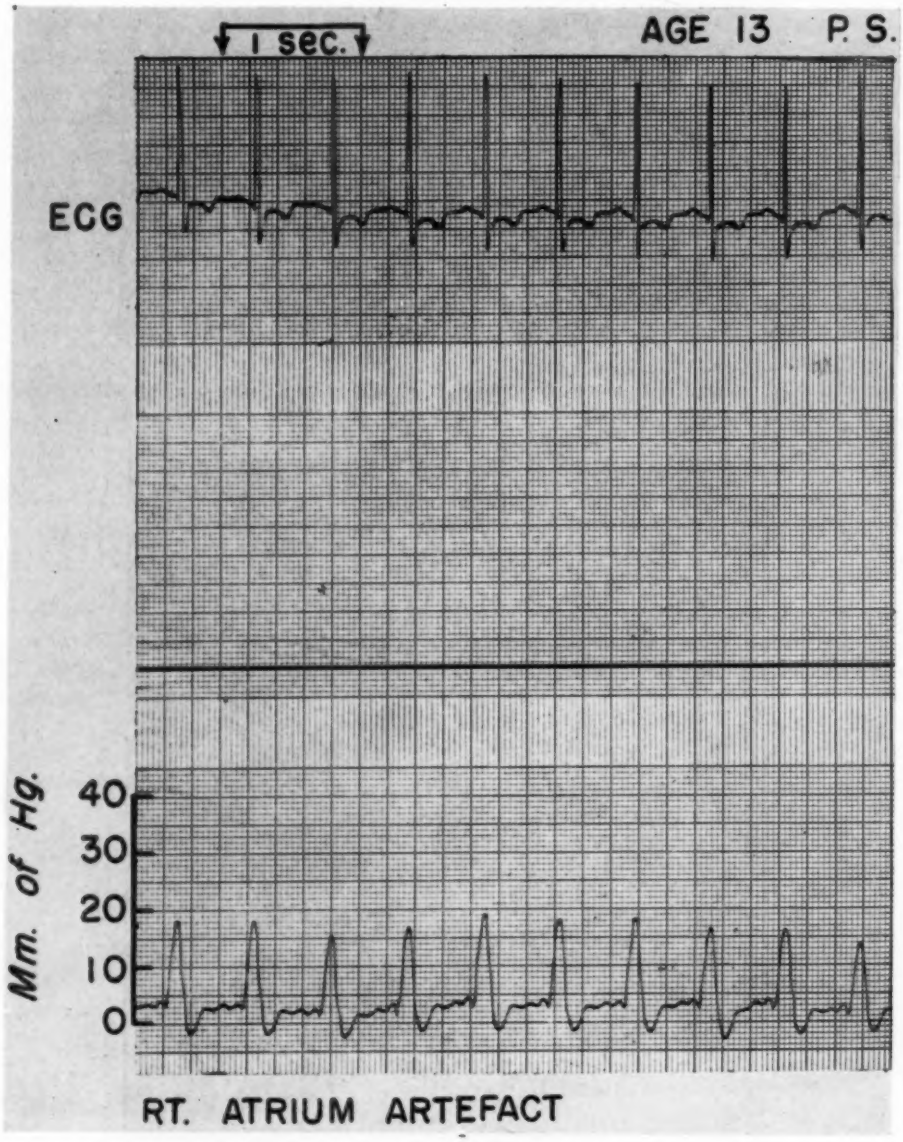


Fig. 6.—Case 11. Artefactual right atrial pressure curve, showing falsely high right atrial systolic pressure peaks of 17 mm. Hg, resulting from catheter movement.

Comment: The rather low oxygen saturation of pulmonary venous blood (87 per cent) in this patient was somewhat puzzling, since pulmonary venous blood is usually saturated 95 per cent or more with oxygen in patients with congenital heart disease.[13] This patient had sickle-cell anemia with a hemoglobin of 8 Gm. per 100 c.c. of blood. The unsaturation of his pulmonary venous blood may be due to the increased alveolar-arterial oxygen tension gradient seen in anemia,[14] and to the abnormal oxygen dissociation curve of sickle-cell anemia.[15]

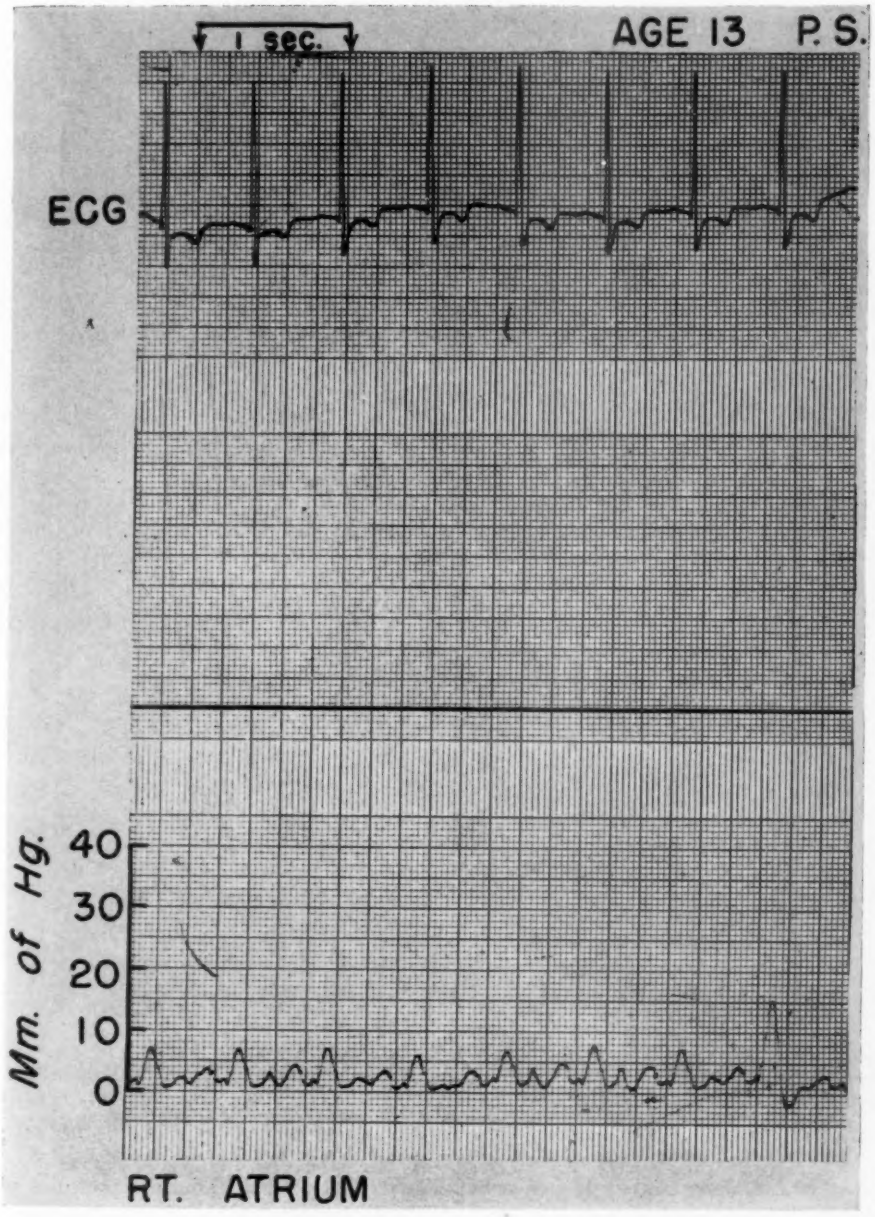


Fig. 7.—Case 11. Right atrial pressure curve, showing atrial systolic pressure peak of 7 mm. Hg. The final atrial systolic wave of this figure is artefactually high.

The difficulty in distinguishing anomalous pulmonary venous drainage from atrial septal defect has been clearly described by Swan, Burchell, and Wood.[16] Not infrequently, it may be impossible to make the distinction by cardiac catheterization alone.

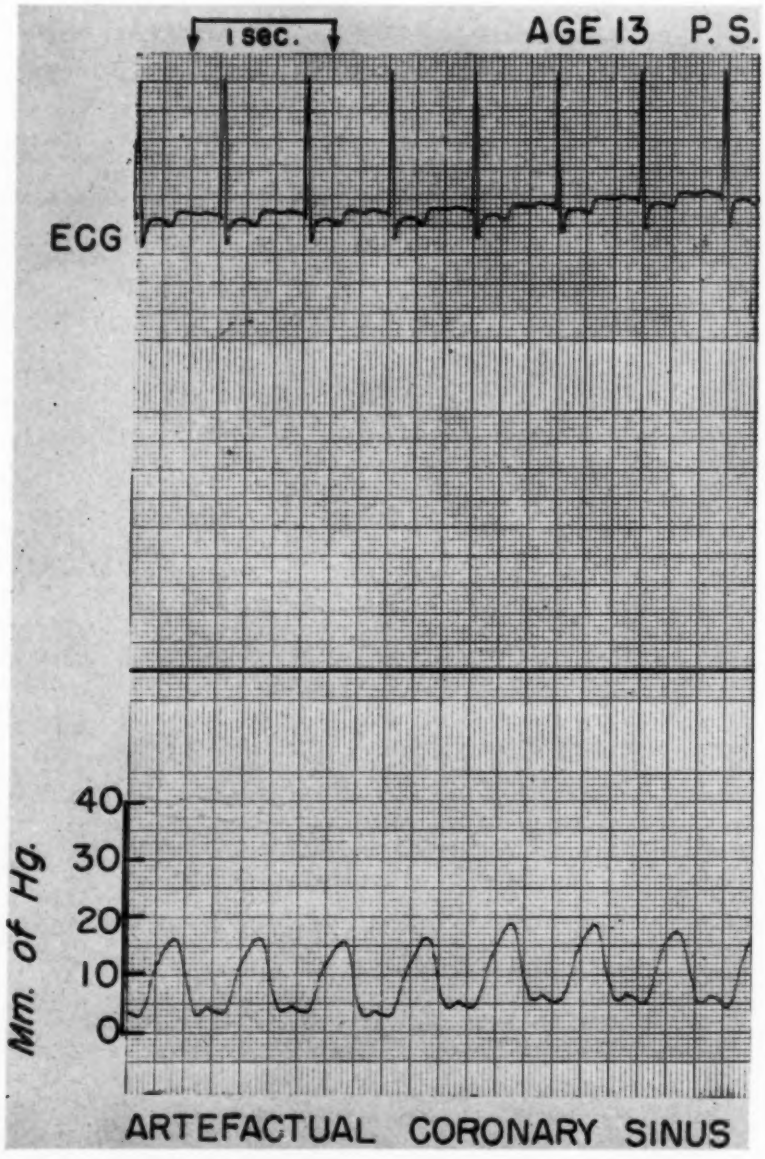


Fig. 8.—Case 11. Pressure curve obtained from catheter tip wedged in a tributary of the coronary sinus, simulating a right ventricular pressure curve. Pressure is 17/4 mm. Hg. The actual right ventricular pressure of this patient was 125/8 mm. Hg.

CASE 11.—*Congenital heart disease; atrial septal defect and pulmonary stenosis; artefactual right atrial and coronary sinus pressure curves:* Two other difficulties in interpretation of cardiac catheterization data are illustrated by a study made June 22, 1955, of a 13-year-old girl with pulmonary stenosis and an atrial septal defect. During the cardiac catheterization, the pressure curve shown in Fig. 6 was obtained when the catheter tip was in the right atrium. It may be seen that the pressure peaks are 17 mm. Hg. A more accurate right atrial pressure curve is shown

in Fig. 7, where it can be seen that the right atrial systolic pressure peak is only 7 mm. Hg. One of the artefactual peaks is shown at the end of the trace in Fig. 7. It is believed that the falsely high pressure peaks are produced by motion of the catheter tip. These artefacts are of importance for two reasons: first, they may cause the right atrial systolic pressure to be read as erroneously high; second, they may, in the haste of performing the procedure, be misinterpreted as a right ventricular pressure curve. In this connection, it may be readily seen that the onset of the artefactual pressure pulses in Fig. 6 occurs well before the beginning of the QRS complex of the electrocardiogram.

In Fig. 8 is shown a pressure record obtained by wedging the catheter tip into a tributary of the coronary sinus in this patient. Here a pressure of 17/4 mm. Hg is seen. This type of recording, obtained by wedging the catheter tip into the coronary sinus or one of its tributaries, may simulate a right ventricular pressure record.[17] Since the position of the catheter in the anteroposterior view obtained by fluoroscopy may also resemble a right ventricular position, confusion may result. The distinction may generally be made by the low oxygen content of coronary sinus blood and by the posterior location of the catheter in the coronary sinus upon lateral fluoroscopy. The right ventricular pressure of this patient was 125/8 mm. Hg.

SUMMARY

By means of illustrative case reports, the following difficulties in interpretation of data obtained by cardiac venous catheterization are described.

1. The diastolic right atrial pressure was found to be several millimeters of mercury higher than diastolic right ventricular pressure in the absence of organic tricuspid stenosis.

2. The diastolic right ventricular pressure was found to be one-third as high as the right ventricular systolic pressure in conditions other than constrictive pericarditis.

3. Right ventricular systolic pressures may be somewhat higher than those in the pulmonary artery in the absence of pulmonary stenosis. Artefactually low pulmonary arterial pressure readings in the presence of pulmonary hypertension resulting from temporary obstruction of the catheter tip may cause an incorrect diagnosis of pulmonary stenosis to be made.

4. Increase in oxygenation of right atrial blood may be produced by a septal defect between the left ventricle and right atrium.

5. The observation of an increase in oxygen content of pulmonary arterial over right ventricular blood requires consideration of a number of possibilities. In addition to patency of the ductus arteriosus some of the other causes are variations in pulmonary flow; ventricular septal defect; anomalous pulmonary arteries; contamination of the sample by pulmonary venous blood, resulting from a peripheral location of the catheter tip.

6. As the probable result of pulmonary valvular insufficiency, patent ductus arteriosus may be associated with an apparently greater increase in oxygenation of right ventricular than of pulmonary arterial blood.

7. When the tip of a cardiac catheter enters a pulmonary vein after entering the cardiac shadow, caution is required to ascertain whether the pulmonary vein drains into the right or the left atrium.

8. The pressure curve obtained by wedging the cardiac catheter tip into the coronary sinus or one of its tributaries may simulate a right ventricular pressure curve.

9. Artefacts in the right atrial pressure curve resulting from motion of the catheter tip may cause a falsely high right atrial systolic pressure reading.

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ELECTROCARDIOGRAPHIC INDICATIONS OF SIGNIFICANT MITRAL INSUFFICIENCY IN PATIENTS WITH MITRAL VALVE DISEASE

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SURGICAL correction of mitral stenosis has become an accepted procedure in selected cases. This has made it important to diagnose preoperatively in such cases the degree of competence of the mitral valve as well as the degree of stenosis. At present our tools for diagnosing significant mitral insufficiency in patients with rheumatic mitral valve disease are imperfect. Thus, many series of mitral commissurotomies report cases in which cardiotomy revealed unexpected predominant mitral insufficiency.[1-9]

The present paper reports some electrocardiographic features of significant mitral insufficiency which came to our attention during the first 126 operations for mitral valvulotomy at The New York Hospital.

METHODS AND MATERIALS

The study was carried out from 1950 through 1954, utilizing the first 126 patients undergoing cardiotomy at The New York Hospital for the purpose of mitral valvulotomy.

Four patients were excluded: one with right bundle branch block, one with associated congenital heart disease, one with no significant mitral valve disease found at operation, and one in cardiac arrest while the heart was open, so that the degree of mitral insufficiency could not be ascertained. Thus, 122 cases were included in the final study. All surgery was performed by one of us (F.G.). At operation, estimation was made of the degrees of mitral stenosis and insufficiency present. Mitral insufficiency was graded 0 to 4 plus, the degrees of positivity representing slight, moderate, considerable, and gross. This estimate is used for purposes of the present study. All patients in this series had either a mitral valve area estimated at 1.5 cm. or less at surgery, or mitral insufficiency of Grade 3 or more. Thus, all patients had either significant mitral stenosis, severe mitral insufficiency, or both.

Each patient had a preoperative electrocardiogram comprising three standard, three unipolar limb, and six unipolar chest leads. This was taken during

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the six months prior to surgery, utilizing a Cambridge string galvanometer electrocardiograph. Leads were standardized in the usual manner and amplitudes in question appropriately corrected. The cardiograms were analyzed regarding (a) rhythm, and (b) amplitudes of S_{V1-4}, and R_{V3-6}. (In leads where amplitudes varied from complex to complex, the greatest amplitude was utilized.)

The series of 122 patients was divided into two groups. Those who had significant mitral insufficiency or who were in some other way predisposed to left ventricular hypertrophy (hereafter designated LVH) formed Group 1; those who had no such predisposition formed Group 2. Predisposition to LVH was considered to exist if patients exhibited one or more of the following:

1. Mitral insufficiency estimated Grade 2 or more at surgery;
2. Preoperative blood pressures consistently exceeding 145 mm. Hg systolic or 95 mm. Hg diastolic;
3. Murmurs which, in conjunction with other findings, were considered indicative or aortic stenosis or insufficiency preoperatively and/or on careful clinical examination up to thirty-five months postoperatively.

RESULTS

We noted that our Group 1 patients had preoperative electrocardiograms possessing in many instances features absent in the Group 2 patients. Thus, certain criteria could be formulated which were met by many of the Group 1 patients, and by few or none of the Group 2 patients. These were as follows:

(a) $S_{V_1} \geqq 10$
(b) $S_{V_2} \geqq 26$
(c) $R_{V_6} \geqq 15$
(d) S_{V_1} or $_{V_2} + R_{V_5}$ or $_{V_6} \geqq 34$

Results using these criteria depended on the cardiac rhythm.

When applied to the sixty-one patients who had auricular fibrillation, the proposed criteria selected twenty-two patients, all of whom fell in Group 1 (e.g., were LVH predisposed). Since there were, altogether, thirty-three Group 1 patients with auricular fibrillation, the criteria thus correctly selected two-thirds of these. There were no false-positive results. These data are shown in Table I,A.

The proposed criteria were unsatisfactory when applied to the sixty-one patients with normal rhythm. There were thirteen such patients in Group 1. Although seven of these had electrocardiograms meeting proposed criteria, the criteria selected a relatively high number of Group 2 patients, e.g., false-positive patients. This is clearly shown in Table I,B.

Table II shows breakdown of the patients with auricular fibrillation according to mode in which predisposed to LVH. The proposed criteria were satisfied by five of the eight fibrillating patients with mitral insufficiency as the sole LVH-predisposing factor. Patients with aortic valve disease as the sole predisposing factor had the lowest incidence of electrocardiograms (seven out of the fourteen) satisfying the criteria.

TABLE I. FULFILLMENT OF PROPOSED CRITERIA IN 122 PATIENTS WITH MITRAL VALVE DISEASE

	PATIENTS PREDISPOSED TO LVH (GROUP 1)	PATIENTS NOT PREDISPOSED TO LVH (GROUP 2)
A. The 61 patients with auricular fibrillation:		
Meet proposed criteria	22	0
Do not meet proposed criteria	11	28
Total	33	28
	Total 61	
B. The 61 patients with normal rhythm:		
Meet proposed criteria	7	17
Do not meet proposed criteria	6	31
Total	13	48
	Total 61	

TABLE II. FURTHER STUDY OF THE 22 PATIENTS WITH AURICULAR FIBRILLATION WHO WERE PREDISPOSED TO LVH: RELATION OF PREDISPOSING FACTOR TO ECG FINDINGS

FACTOR PREDISPOSING TO LVH	TOTAL CASES	ECG's MEETING PROPOSED CRITERIA
Aortic valve disease	14	7
Mitral insufficiency	8	5
Hypertension	1	1
Mitral insufficiency plus aortic valve disease	7	7
Mitral insufficiency plus hypertension	1	1
Aortic valve disease plus hypertension	2	1
Total	33	22

Sensitivity of the criteria in the patients with auricular fibrillation is shown in Table III. The most sensitive were $S_{V_{1,2}} + R_{V_{5,6}} \geqq 34$, and $R_{V_6} \geqq 15$.

TABLE III. SENSITIVITY OF PROPOSED CRITERIA IN THE 33 LVH-PREDISPOSED PATIENTS WITH AURICULAR FIBRILLATION

CRITERION	(A) $S_{V_1} \geqq 10$	(B) $S_{V_2} \geqq 26$	(C) $R_{V_6} \geqq 15$	(D) $S_{V_{1,2}} + R_{V_{5,6}} \geqq 34$	ONE OR MORE OF A, B, C, OR D
ECG's satisfying the criterion	5	3	11	15	22

These criteria selected, with statistically significant specificity, those fibrillators with LVH predisposition ($p < .01$ and $p < .02$, respectively). Too few patients satisfied the S_{V_1} and S_{V_2} criteria to allow statistical testing.

DISCUSSION

1. *Corroborative Data.*—Bateman and January,[10] in a recent publication, have reported on electrocardiographic findings in a series of ninety-two patients subjected to thoracotomy for surgical relief of mitral stenosis. They noted that the mean heights of S_{V_1}, R_{V_5}, and/or R_{V_6} were greater in those patients with significant mitral insufficiency than in those with pure mitral stenosis. Analysis of their figures reveals that, as in the present study, the S_{V_1}, R_{V_5}, and R_{V_6} values in the patients with mitral insufficiency were nevertheless often not great enough to satisfy Sokolow's* criteria for left ventricular hypertrophy. Since the authors did not break down their cases according to rhythm, further comparison of their data with ours cannot be carried out.

2. *Auricular Fibrillation vs. Normal Rhythm.*—The authors have no ready explanation why so many false-positive results were obtained in the group with normal rhythm, using the proposed criteria. The discrepancy here between our patients with auricular fibrillation and those in normal rhythm is striking (see Table IV). Possibly these patients are not "false positives" and we are merely missing the diagnosis of aortic valve disease in many of them, or the auricular fibrillation series may be biased. We think this latter unlikely since the more sensitive criteria can already be shown to be statistically valid in the patients with auricular fibrillation (see above).

TABLE IV. FURTHER ANALYSIS OF PROPOSED CRITERIA: RELATION OF FALSE-POSITIVE RESULTS TO HEART RHYTHM

RHYTHM	TOTAL PATIENTS MEETING PROPOSED CRITERIA	"FALSE POSITIVES," E.G., PATIENTS NOT PREDISPOSED TO LVH
Auricular Fibrillation	22	0
Normal rhythm	24	17

3. *Value of the Criteria in Diagnosing Mitral Insufficiency.*—Thirteen of the sixteen patients with auricular fibrillation (AF) and significant mitral insufficiency met the proposed criteria. This includes five out of eight in whom mitral insufficiency was the sole factor predisposing to LVH. Only six of these sixteen patients satisfied the criteria of Sokolow and Lyon for left ventricular hypertrophy. It might be reasoned that the existence of the proposed criteria in a patient with mitral valve disease and auricular fibrillation, without aortic valvular murmurs or hypertension, argues strongly for significant mitral insufficiency. We believe this is true, with the reservations that: (a) aortic

*The criteria of Sokolow and Lyon for left ventricular hypertrophy have recently been shown to be the most sensitive of existing electrocardiographic indices for diagnosing left ventricular hypertrophy.[11,12]

valve disease may occasionally cause electrocardiographic changes before it is clinically detectable, and (b) the future occurrence of some false-positive results in patients with AF cannot be excluded.

The great majority (fifteen out of seventeen) of our patients who had significant mitral insufficiency in association with some degree of mitral stenosis had auricular fibrillation. Gorlin[13] noted a similarly high incidence of AF in his patients with mitral insufficiency accompanying mitral stenosis. Thus, the bulk of patients with rheumatic mitral stenosis who have significant mitral insufficiency apparently fall in the rhythm group (AF) to which the proposed electrocardiographic criteria are applicable. (But patients with "pure" mitral insufficiency, e.g., no stenosis whatsoever, including no murmur of stenosis, appear to have normal rhythm more frequently than auricular fibrillation.[14])

These criteria are not presented as indicators of left ventricular hypertrophy. Left ventricular hypertrophy is an anatomic diagnosis, proof for which, in patients coming to mitral commissurotomy, is extremely hard to document. Thus, the chest x-ray at times fails to detect early or minimal left ventricular hypertrophy, and at other times is complicated by multichambered cardiac enlargement. The surgeon's estimate of left ventricular thickness at operation is necessarily subject to considerable error. Autopsy studies of these patients, allowing correlation of left ventricular thickness with the electrocardiographic picture shortly before death, may be necessary to provide the answer to this problem.

Meanwhile, the present study presents a purely empirical correlation of certain electrocardiographic findings with the presence of significant mitral insufficiency, hypertension, and/or aortic valve disease in patients with advanced mitral valve disease.

SUMMARY AND CONCLUSIONS

1. The first 126 patients undergoing cardiotomy at The New York Hospital for mitral commissurotomy were analyzed regarding their preoperative electrocardiograms.

2. From this series, electrocardiographic criteria were derived which, in many instances, accurately selected those patients with significant mitral insufficiency, hypertension, and/or aortic valve disease. These are as follows: (a) $S_{V_1} \geqq 10$, (b) $S_{V_2} \geqq 26$, (c) $R_{V_6} \geqq 15$, and (d) S_{V_1} or $_{V_2} + R_{V_5}$ or $_{V_6} \geqq 34$.

3. In the presence of auricular fibrillation, these criteria were entirely specific, e.g., they occurred only in patients thus predisposed in some way to left ventricular hypertrophy.

4. The criteria were unsatisfactory when applied to cases with normal rhythm because they yielded a high number of false-positive results.

5. Rationale and applicability of the criteria are discussed, with especial reference to their value in diagnosing significant mitral insufficiency.

The authors are indebted to Drs. Hugh Luckey and Harold J. Stewart for their thoughtful consideration and wise counsel concerning the data presented.

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ELECTROCARDIOGRAPHIC CHANGES IN ARTIFICIAL HIBERNATION

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THE electrocardiographic records of a group of individuals submitted to the procedure of artificial hibernation, following the technique of Laborit and Huguenard,[24,25] with slight modifications, have been studied. They presented some particular characteristics distinguishing them from those obtained under other physiologic and pathologic conditions, the changes observed being closely related to the lowering of the body temperature.

MATERIAL AND METHODS

Electrocardiograms were taken in ten patients (eight men and two women) whose ages were between 6 and 47 years who were submitted to artificial hibernation. To induce this state, drugs 3277, 2987, and 4560 of Rhone Poulenc (derived from phenotiazin) were specially used in the form of "lythical cocktails" as proposed by Laborit and Huguenard.[24,25] After the neuroendocrine disconnection was obtained by the action of these agents, cold was applied by means of ice bags in the hepatic and precordial regions and in the regions of the main arteries. In eight of the cases, the records were serially obtained at different temperatures.

The procedure was applied for different reasons: in five cases, previous to major neurosurgical operations; in two, for serious cranial trauma (a bullet wound in a suicidal intent); and in three, serious psychiatric cases. In none of the ten cases were observed untoward accidents imputable to the artificial hibernation, although all the patients except one were submitted to a temperature of 30° C. or less, reaching in one case (Fig. 5) 22°; only five of the cases were in a satisfactory clinical condition when hibernated.

They were maintained in this state during a period of two to six days, reaching in some cases a very significant reduction of the temperature (in one patient from 38° C. to 22° C., and in another from 40° C. to 24° C.). For technical reasons it was not always possible to obtain records in the extreme temperatures.

The records were obtained with two direct-recording electrocardiographs simultaneously, data carefully measured at brief intervals of the respiratory fre-

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quency, and blood pressure was obtained. The general morphology of the electrocardiographic waves was studied, and the P-R, QRS, and Q-T intervals, Q-T/T-Q relation, and the variations of the electrical axes were determined. The Q-T interval was corrected according to the variations of the cardiac rate, applying the formula of Bazett,[4] modified by Taran and Szilagyi[38]: $Q\text{-}T_c = Q\text{-}T/\sqrt{R\text{-}R}$.

RESULTS

All the patients showed significant modifications of the electrocardiographic record when compared with the record obtained in basal conditions, or in the first periods of the hibernation, or at least (in four cases) with respect to normal characteristics and values.

The duration of the P-R interval increased from 0.01 to 0.1 second in all the cases in which it could be compared in basal conditions and at different temperatures, except as in Fig. 6, in which at 31° C. it was longer than at 28° C. These changes were accompanied by simultaneous modifications of the P wave, which was, generally, larger the longer the P-R interval and the lower the temperature.

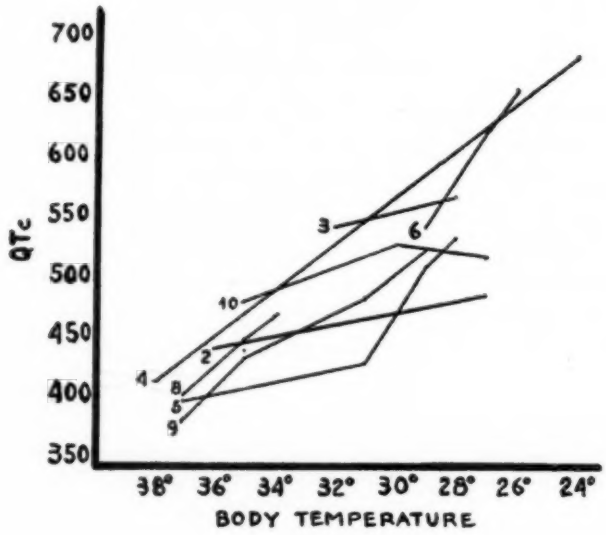

Fig. 1.

The QRS complex became larger as the temperature and pulse decreased; but variations in potentials were inconstant. Nevertheless, in most cases a marked increase of the potentials was observed.

The voltage of the T wave decreased in the first period of hibernation, followed by an increase of its potential during the period of stabilization. Transitory inversion was frequently seen.

Variable changes appeared in the S-T interval, the most constant being a slight elevation with ascent of the junction in marked hypothermia.

The Q-T interval was considerably increased in all cases, this prolongation varying between 0.075 and 0.345 second, the increase being, in general, in relation to the descent of the temperature (Fig. 1). Corrected in relation to heart

TABLE I

CASE	CLINICAL DATA				ELECTROCARDIOGRAM				
	P	B.P.	R.R.	B.T. (DEGREES C.)	P-R	QRS	Q-T	Q-T$_c$	E.A. (DEGREE)
1	106	100–80	44	34	0.145	0.08	0.360	0.494	−30
2	166	—	32	36	0.09	0.08	0.270	0.449	+83
	90	70–	20	27	0.16	0.11	0.400	0.486	+71
3	106	—	29	32	0.15	0.09	0.410	0.548	+88
	80	80–	24	28	0.16	0.10	0.500	0.572	+85
4	140	95–50	30	38	0.155	0.07	0.275	0.420	−68
	75	90–	18	24	0.18	0.09	0.620	0.690	−50
5	116	145–90	20	37	0.14	0.10	0.290	0.404	+74
	88	130–85	20	31	0.18	0.12	0.360	0.435	+54
	64	90–65	18	27	0.24	0.12	0.500	0.515	—
	70	90–65	12	26	0.16	0.12	0.500	0.539	+75
6	115	90–70	23	29	fib.	0.12	0.395	0.548	+11
	75	80–	17	27	0.15	0.12	0.560	0.625	+15
	68	—	15	26	0.24	0.13	0.620	0.660	—
7	106	100–70	17	30	0.13	0.08	0.365	0.486	—
8	58	150–95	26	37	0.16	0.10	0.415	0.408	+ 5
	102	—	23	35	0.19	0.12	0.340	0.452	+51
	88	130–90	20	34	0.19	0.12	0.390	0.472	+35
	65	120–85	—	29	0.20	0.14	0.505	0.526	+46
9	97	130–80	27	37	0.14	0.09	0.305	0.386	+52
	75	90–60	11	35	0.14	0.09	0.390	0.436	+48
	102	85–60	10	31	0.15	0.09	0.340	0.444	+49
	95	80–	10	29	0.15	0.09	0.390	0.496	+49
10	120	120–80	22	35	0.14	0.09	0.330	0.465	+80
	88	100–70	16	30	0.15	0.12	0.440	0.532	+82
	65	80–60	10	27	0.17	0.18	0.490	0.522	+80

P = Pulse rate, B.P. = Blood pressure, R.R. = Respiratory rate, B.T. = Body temperature, and E.A. = Electrical axis.

rate ($Q\text{-}T_c$) it showed an increase varying between 0.024 and 0.270 second (Table I).

The electrical axis was slightly modified in all the patients, with a tendency to the horizontal. In Fig. 9 the record showed a change to the vertical of the axis with the descent of the body temperature, but it must be noted that the basal record was taken in an unfavourable position for technical reasons (catatonic patient). Nevertheless, in this patient with the descent of the body temperature from 35° C. to 29° C., the electrical axis was slightly more horizontal.

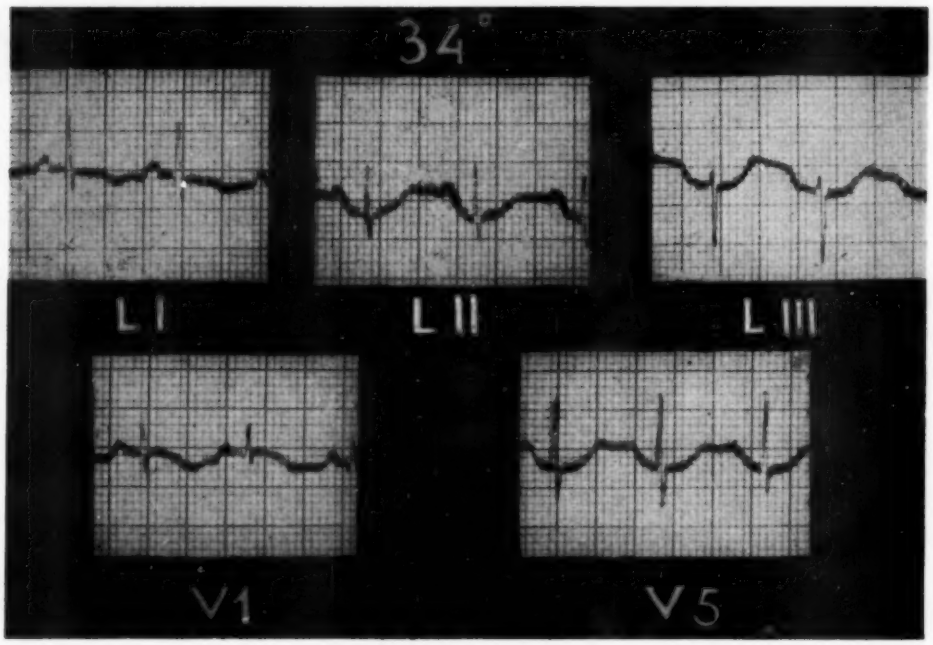

Fig. 2.—Record obtained at 34° C. axillar temperature. Sinus tachycardia of 106 beats per minute. The junction is isoelectric, but the S-T interval is prolonged and the T wave is negative in L_I and V_1, and positive in L_{II}, L_{III} and V_5 being of great voltage, the following P wave starting in its descending limb. It is difficult to measure the Q-T interval; in L_{III} it lasts 0.360 ($Q\text{-}T_c$:0.494), the notch indicates the starting of the following P wave.

No significant changes were observed in the morphology of the P wave or the QRS complex, except in Fig. 11 in which, at 29° C., a transitory right bundle branch block appeared, which increased until the temperature reached 27° C., and in Fig. 6 in which a similar heart block was observed, also transitory, during a heart catheterization made at 27° C.

The prolongation of the Q-T interval, together with the increase of the electrical area of the T wave, had in most cases a curve similar to that appearing during the administration of quinidine and other drugs of similar effect. The changes observed were, however, much more pronounced in our patients and were strictly related to the lowering of the body temperature.

With regard to the occurrence of arrhythmias during hibernation, a transitory auricular fibrillation was observed, in one case, when the temperature reached 29° C. It stopped suddenly, even though we brought the body tempera-

ture down to 26° C. However, at 27° C. supraventricular extrasystoles were observed.

It must be noted that the existence of tachycardia is very frequently found (up to 166 per minute) during the induction period. After that the rate becomes more regular with a tendency to bradycardia when a state of really profound hibernation is attained.*

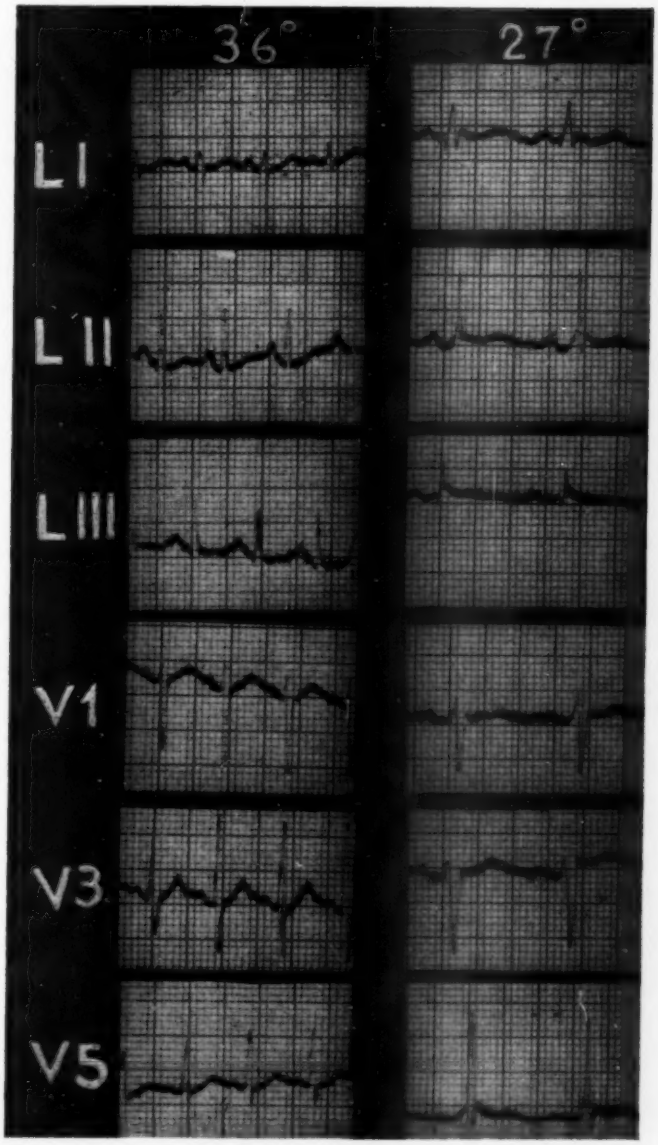

Fig. 3.—36° C.: Sinus tachycardia (166 beats per minute). Flattened T wave in the classic leads; 27° C.: The rate decreased to 90 beats per minute. The S-T interval is elevated more or less 1 mm. in L_I, L_{II}, L_{III}, and V_5. The T wave is flattened, large, and the Q-T interval measures 0.400 sec. ($Q\text{-}T_c$: 0.486).

*The arrhythmias observed are only mentioned because they will be the subject of a following article.

DISCUSSION

As already expressed in previous work,[41,42] during artificial hibernation the activity of the heart is depressed, together with most of the organic functions. The electrocardiographic changes concorded with the diminution of the oxygen consumption and of the work of the left ventricle, and consisted principally in prolongation of the Q-T interval and bradycardia, together with marked changes in the configuration of the records.

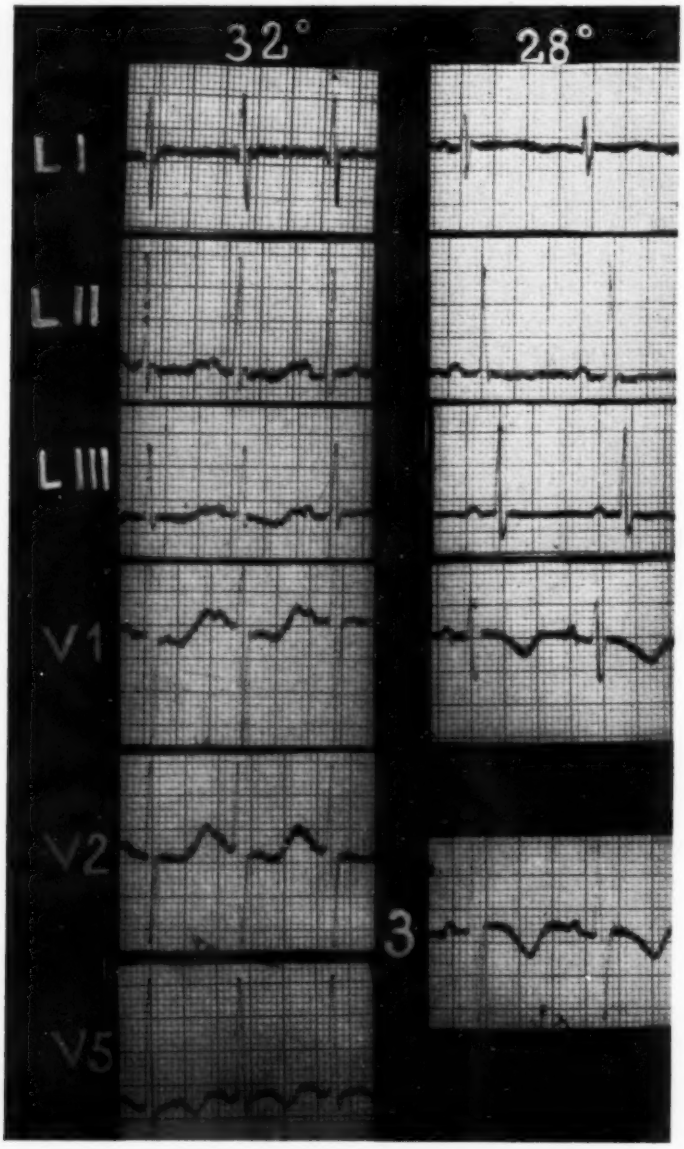

Fig. 4.—32° C.: Sinus tachycardia (106 beats per minute). There is a flattened T wave in L_I, and it is negative in L_{II}, L_{III}, and V_5, and it is diphasic (negative-positive) in V_1 and V_2. 28° C.: Rate: 80 beats per minute, isoelectric S-T interval; T wave flattened in L_I, L_{II}, L_{III}, and negative in V_1 and V_2. The Q-T interval measures 0.500 sec. ($Q\text{-}T_c$:0.572).

Similar changes have been observed in anesthetized animals submitted to cold. Smith[34] observed in patients submitted to cold a widening of the QRS complex and an increase in the duration of the S-T interval, and attributed the cases of ventricular fibrillation to diminution of the cardiac output and consequent myocardic anoxia. Others[26] think that it is the result of the anoxia determined by the descent of the oxyhaemoglobin's dissociation capacity.

Clark[12] found, in the frog, bradycardia and a reduction of the mechanical strength of the cardiac contraction, but without observing a strict relation be-

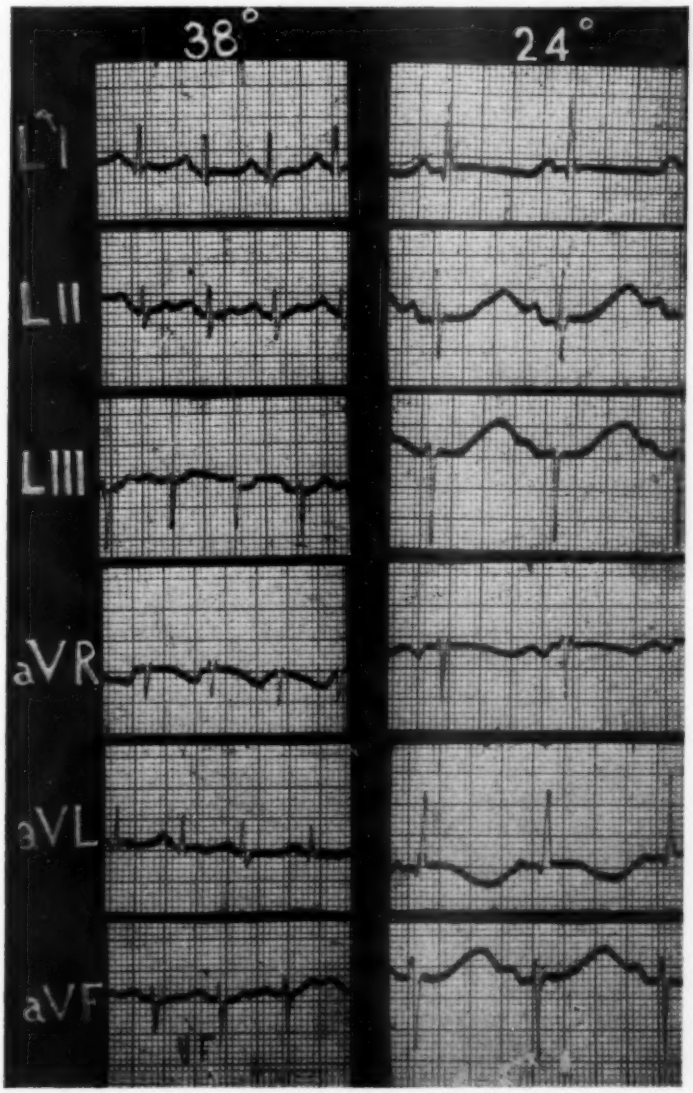

Fig. 5.—38° C.: Sinus tachycardia (140 beats per minute). Flattened T wave with isoelectric S-T interval. 24° C.: Heart rate greatly diminished (75 beats per minute), S-T interval slightly elevated in L_I and aV_L, isoelectric T wave in L_I, but positive in L_{II}, L_{III}, and aV_F; in aV_L it is negative, of great voltage, large, and very prolonged. The next P wave starts in the descending limb of the preceding T wave. The Q-T interval measures 0.620 ($Q\text{-}T_c$:0.690) (see text) (Fig. 5).

tween the heart rate and the descent of the body temperature. On the other hand, Hamilton, Driebach, and Hamilton[18] found a lineal relation between cold and heart rate in rats and small cats.

Barcroft[2] (cited by Lange and associates[26]) found a decisive influence of the body temperature in the oxygen utilization, believing (Lange and associates) that the changes in the T wave are due to anoxia, and the changes in rate and conduction to the direct action of cold.

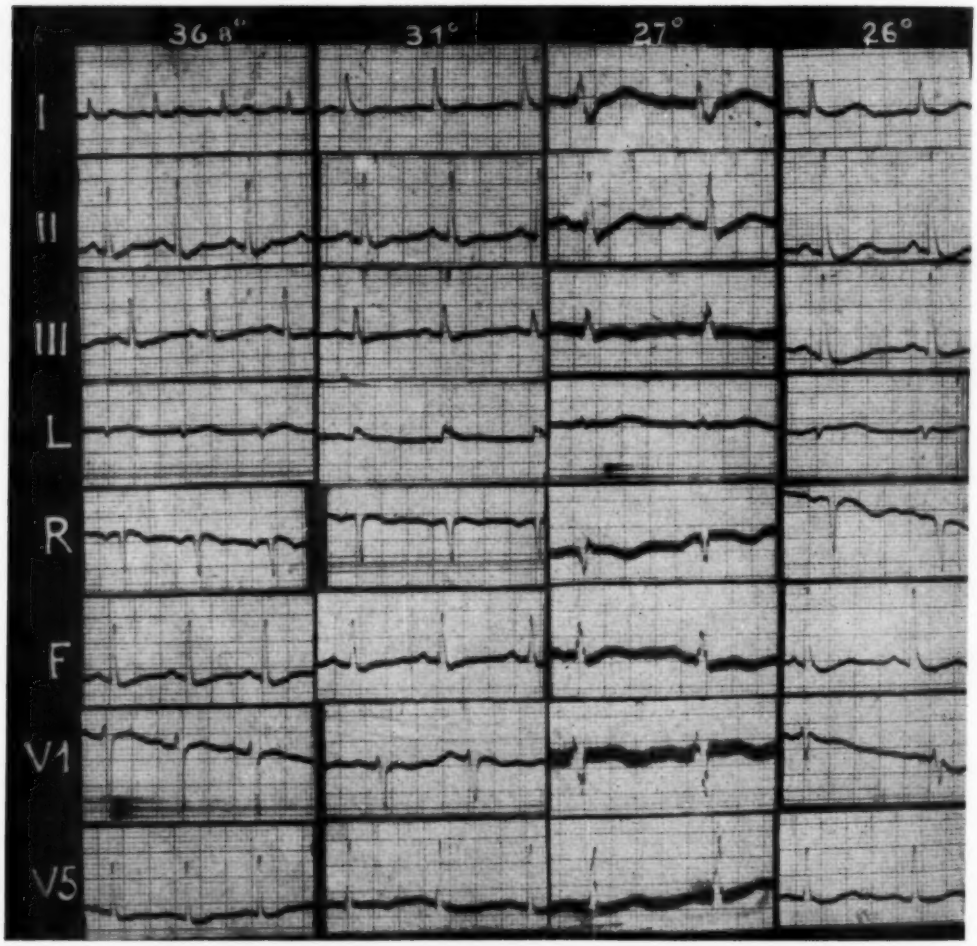

Fig. 6.—36.8° C.: Sinus tachycardia, depressed junction, flattened T wave in all leads. 31° C.: Rate: 88 beats per minute. The depressed junction persists the same as the flattened T wave. 27° C.: Sinus bradycardia (64 beats per minute). First degree of auriculoventricular heart block (P-R:0.24 sec.), large S wave, the type of a right bundle branch block in L_1 that disappears in the following leads (this record was obtained at the moment of the intracardiac catheterization). The Q-T interval measures 0.500 ($Q\text{-}T_c$:0.515). 26° C.: The heart rate is 70 beats per minute. There is a depressed junction, but the T wave is of increased voltage, large, rounded, and the Q-T interval measures 0.500 ($Q\text{-}T_c$:0.539). See text.

The changes that occur in man, partly shown by Cahn, Melon, and Dubrasquet,[7] are not really new, because similar alterations have been seen in other states. There exists considerable evidence (Churchill-Davidson and associates[11]) showing that cold may cause serious arrhythmias and even death.

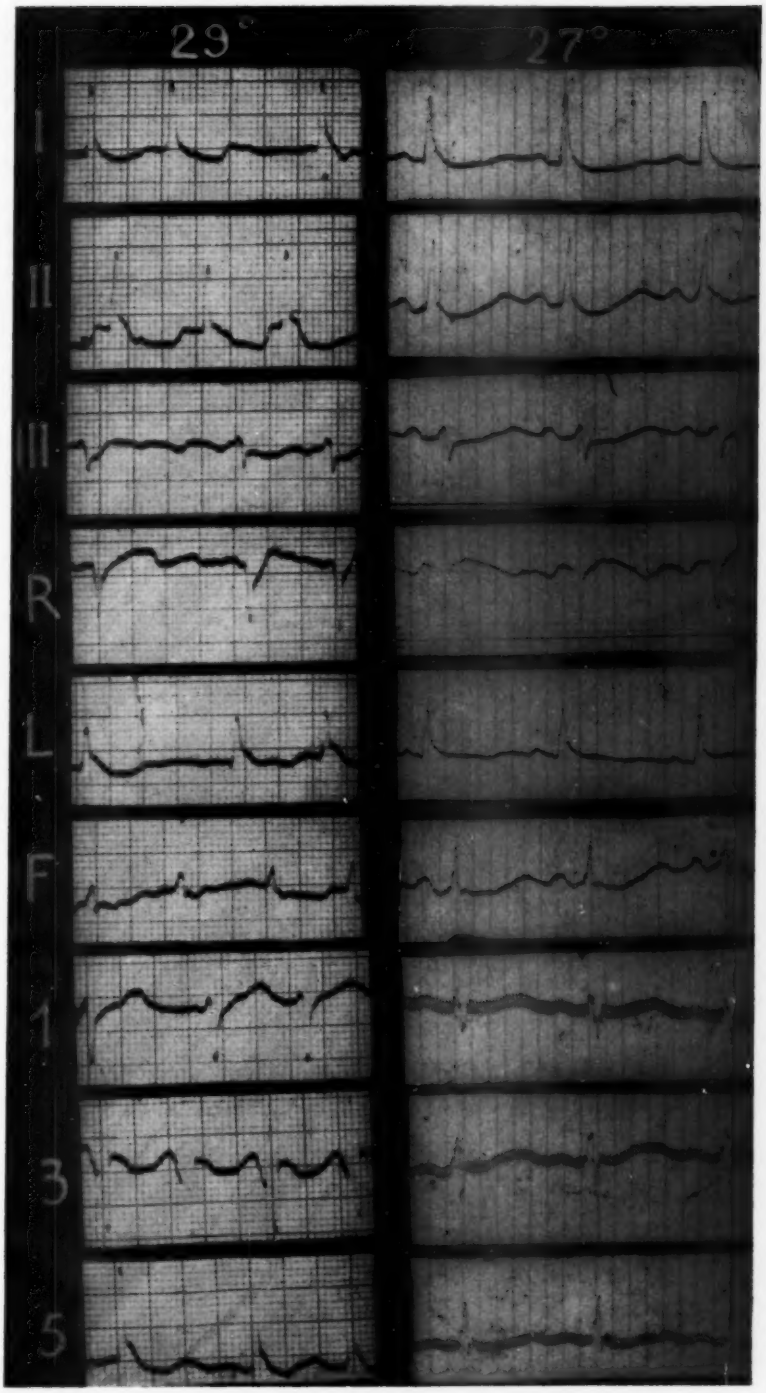

Fig. 7.—29° C.: Auricular fibrillation. Complete arrhythmia with an approximate heart rate of 115 beats per minute. The irregularity of the base line makes the study of the S-T interval and T wave difficult. The T wave is negative in L_I, L_{II}, aV_L, and V_5. 27° C.: Sinus bradycardia, the P-R interval is 0.18 sec., the P wave large, of 0.12 sec., the S-T interval is concave, depressed, and is continued with the diphasic negative-positive T wave in L_I, L_{II}, negative in aV_L and positive in aV_F, V_1, V_3, and V_5. The Q-T interval measures 0.560 ($Q\text{-}T_c$:0.625).

Kossmann,[23] in hypothermia, finds a prolongation of the electrical systole and of the T wave, and a depression of the S-T interval, and in four of the nine patients, auricular fibrillation, while Hook and Stormont[20] find a prolongation of the P-R interval and of the QRS complex, and modifications of the S-T interval.

Hypopotassemia (Thomson,[39] Nadler and colleagues,[31] Henderson,[19] Bellet and colleagues,[5] Engel and colleagues,[15] Ernstene and Proudfit,[16] and Yu[44]) causes a prolongation of the Q-T interval with a flattening and rounding of the T wave. These changes differ from those caused by hypocalcemia (Barker, Johnston and Wilson,[3] Ernstene and Proudfit,[16] Carter and Andrus,[9] and White and Mudd,[43]) which causes a prolongation of the Q-T interval at the expense of a long rectilinear S-T interval with a distant T wave of practically normal aspect.

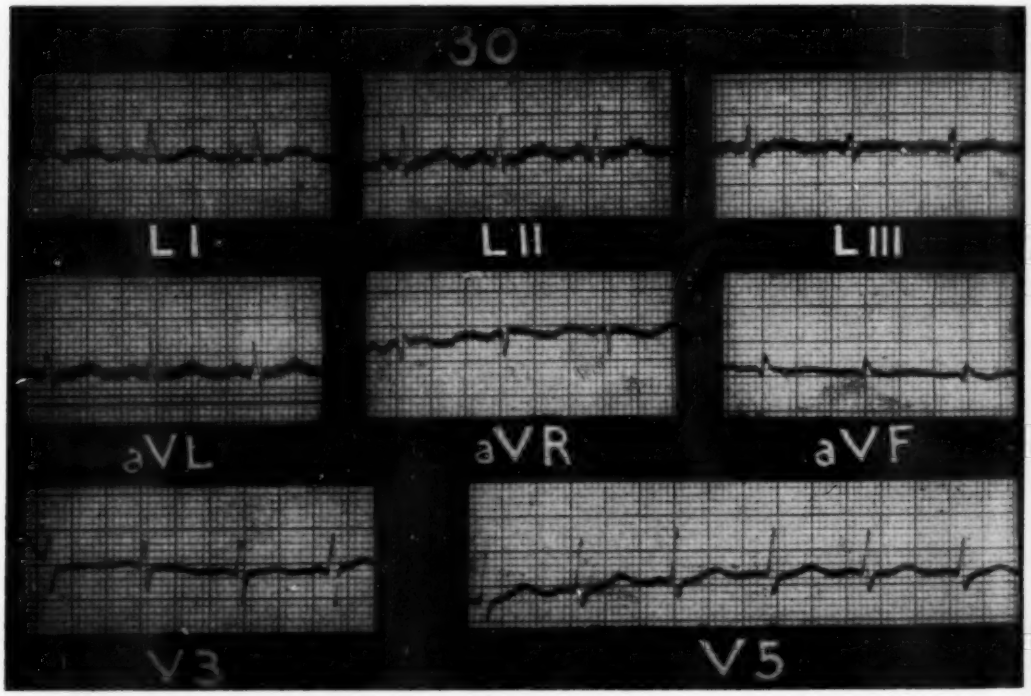

Fig. 8.—Record obtained at 30° C., axillar temperature (cranial trauma, 6-year-old child). Sinus tachycardia, large and round T wave; the Q-T interval is of 0.365 sec. ($Q\text{-}T_c$:0.486).

Studies by various authors (Jung and Jantz,[22] Martin and Wertmann,[29] Ljung,[28] and McAllen[30]) cast doubts upon the validity of these concepts, and, according to Lepeschkin and Surawicz,[27,37] the Q-T interval in hypopotassemia is normal, attributing the previously obtained results to errors in the measurements. These authors affirm that, in this state, the U wave appears as the T wave, because the flattened T wave is accompanied by a visible increase in the voltage of the U wave; consequently, the measured interval would really be the Q-U interval. For them, a real prolongation of the Q-T interval only occurs when hypopotassemia is accompanied by hypocalcemia, also accompanied by an increased Q-U interval.

Similar doubts arise when considering the findings of Stewart and associates,[35] Stoll and Ninewitz,[36] and Perelson and Cosby[32] in periodic familial paralysis, because hypopotassemia also exists in this condition.

However, in our hibernated patients, a real prolongation of the Q-T interval existed (even if phonocardiographic records were not taken[27,37]) since it was observed also in Lead aV_L where U wave[27] is not normally determinable. At any rate, the records were characteristic in the terminal waves.

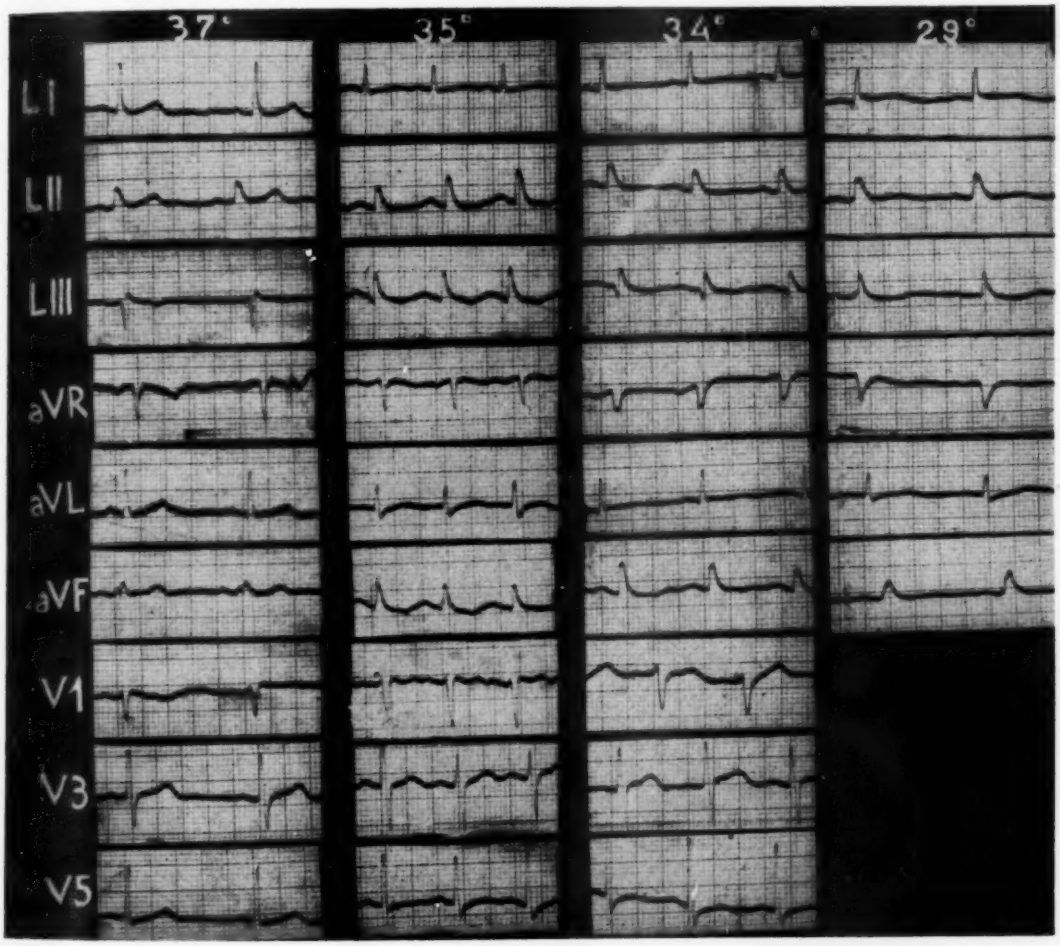

Fig. 9.—37° C.: Sinus bradycardia of 58 beats per minute (record obtained before the artificial hibernation). 35° C.: Sinus tachycardia (102 beats per minute). Flattening of the T wave in L_I, negative in L_{II}, L_{III}, and aV_F. 34° C.: The heart rate has decreased (88 beats per minute), while the abnormalities observed in the S-T interval and T wave persist. 29° C.: Sinus bradycardia, very flattened T wave making the measurement of the Q-T interval difficult. The ending of the T wave can be more or less precisely visualized in L_{II}, and in aV_L, and in these leads the Q-T interval measures approximately 0.505 ($Q\text{-}T_c$:0.526).

Ippolito, Blier, and Fox[21] found inverted and enlarged T waves, together with an enlarged Q-T interval, in cases of extreme bradycardia. These changes cannot be compared to our findings, because in the hibernated patients there was no heart block nor the extreme bradycardia described by these authors.

Our observations cannot be compared to those of Byer, Ashman, and Toth[6]

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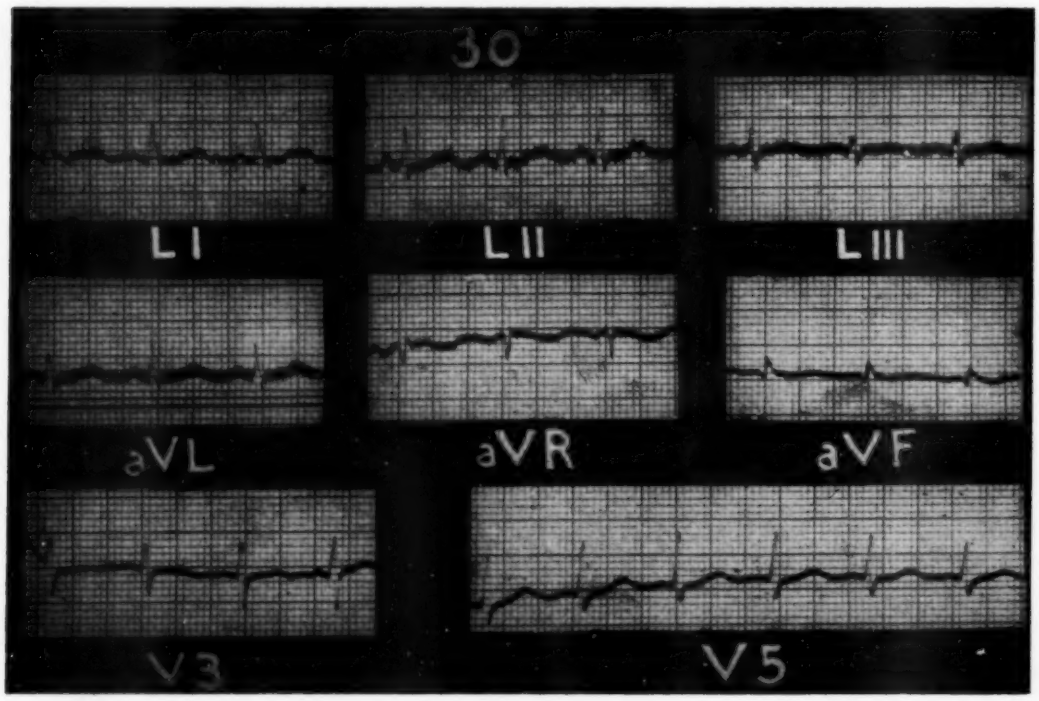

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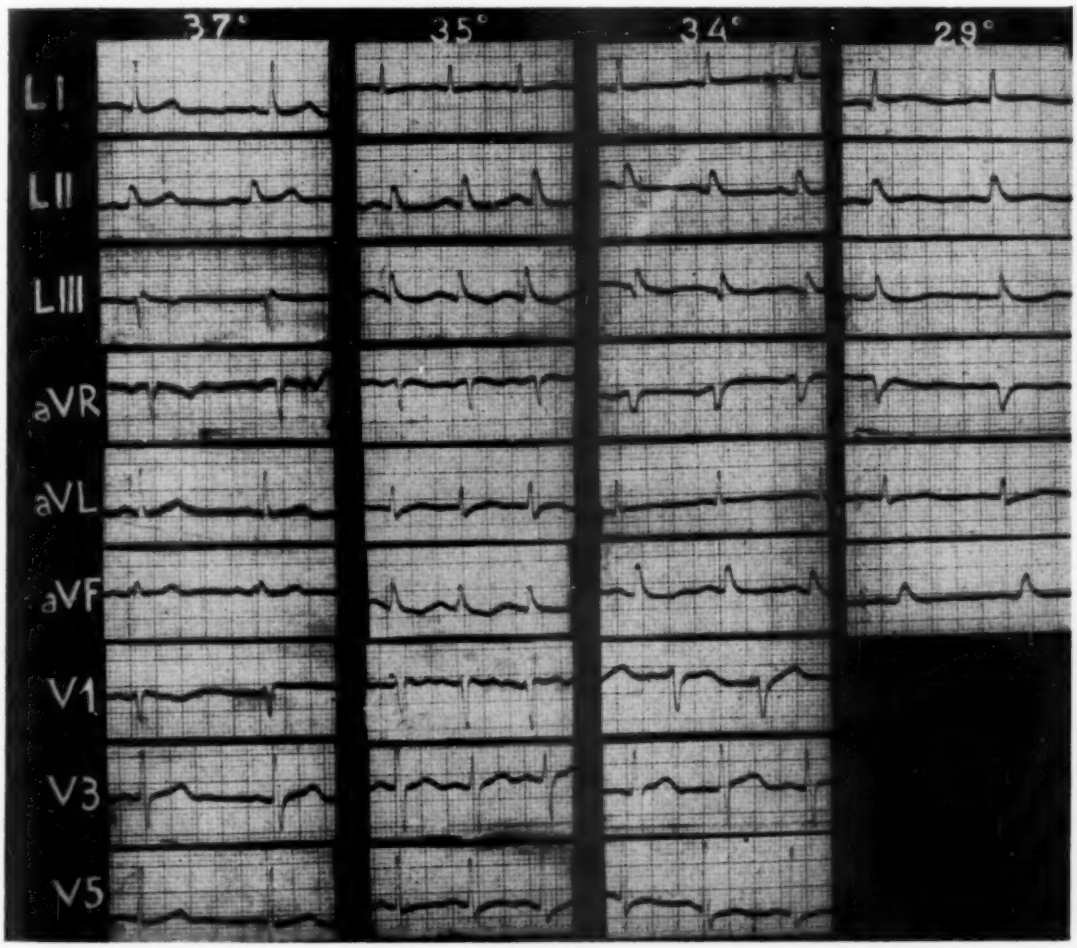

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in the first phase of myocardial infarction, especially because of great differences in the morphology of the T wave, nor to those of Fox, Weaber, and March[17] in a case of aberrant atrioventricular conduction due to the action of procaine amide, a drug which was not used in the hibernated patients. In one of our patients quinidine was injected because of auricular fibrillation without causing any significant change in the Q-T interval or the general morphology of the record (Fig. 7).

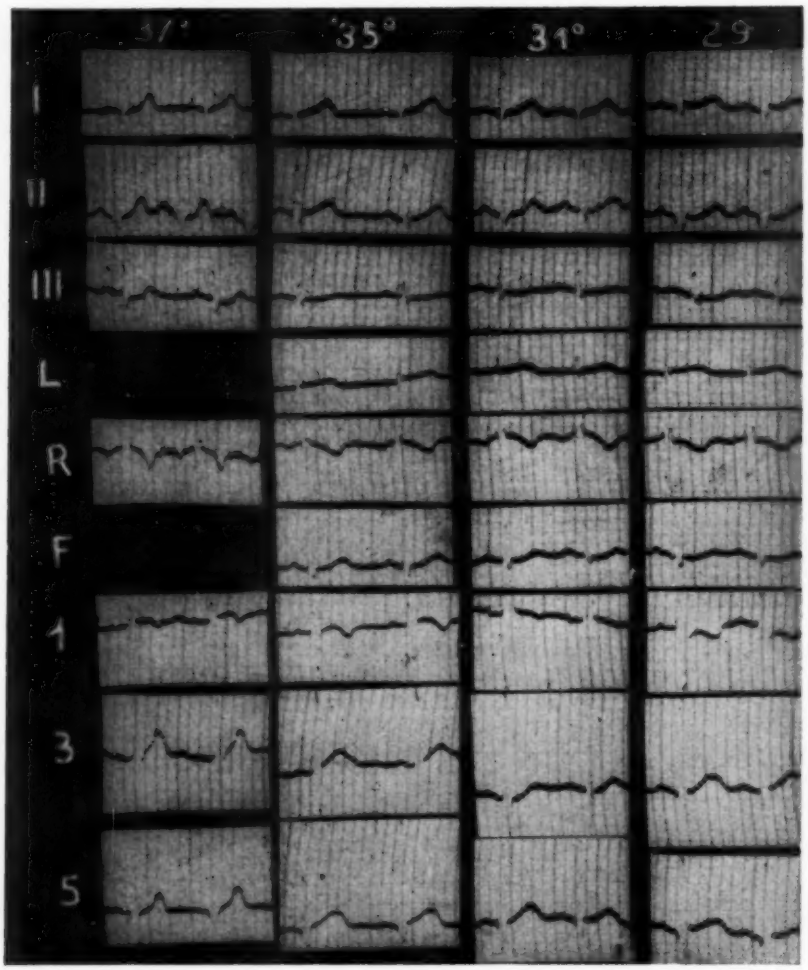

Fig. 10.—37° C.: Record obtained before artificial hibernation. Slight sinus tachycardia, isoelectric S-T interval and T wave of normal voltage. 35° C.: The heart rate has decreased (75 beats per minute), the S-T interval is slightly elevated, and the T wave is enlarged and rounded. 31° C.: Slight sinus tachycardia (102 beats per minute). 29° C.: The heart rate has decreased. A slight elevation of the S-T interval persists and the T wave is even larger and more rounded (see text).

Finally, in undernourished patients, similar modifications of the Q-T interval have been found. Ellis[14] and Cardozo and Eggink[8] found the Q-T interval prolonged in relation to the cardiac cycle in extremely undernourished patients in the absence of accentuated bradycardia. The correct measurement of the Q-T interval was somewhat difficult because the superimposed P wave notched

the descending limb of the T wave. The electrocardiographic records presented by Ellis are similar to those obtained in our artifically hibernated patients.

On the other hand, Simonson, Henschel, and Keys,[33] in experimental studies on prolonged hyponutrition, found a prolongation of the Q-T during the re-

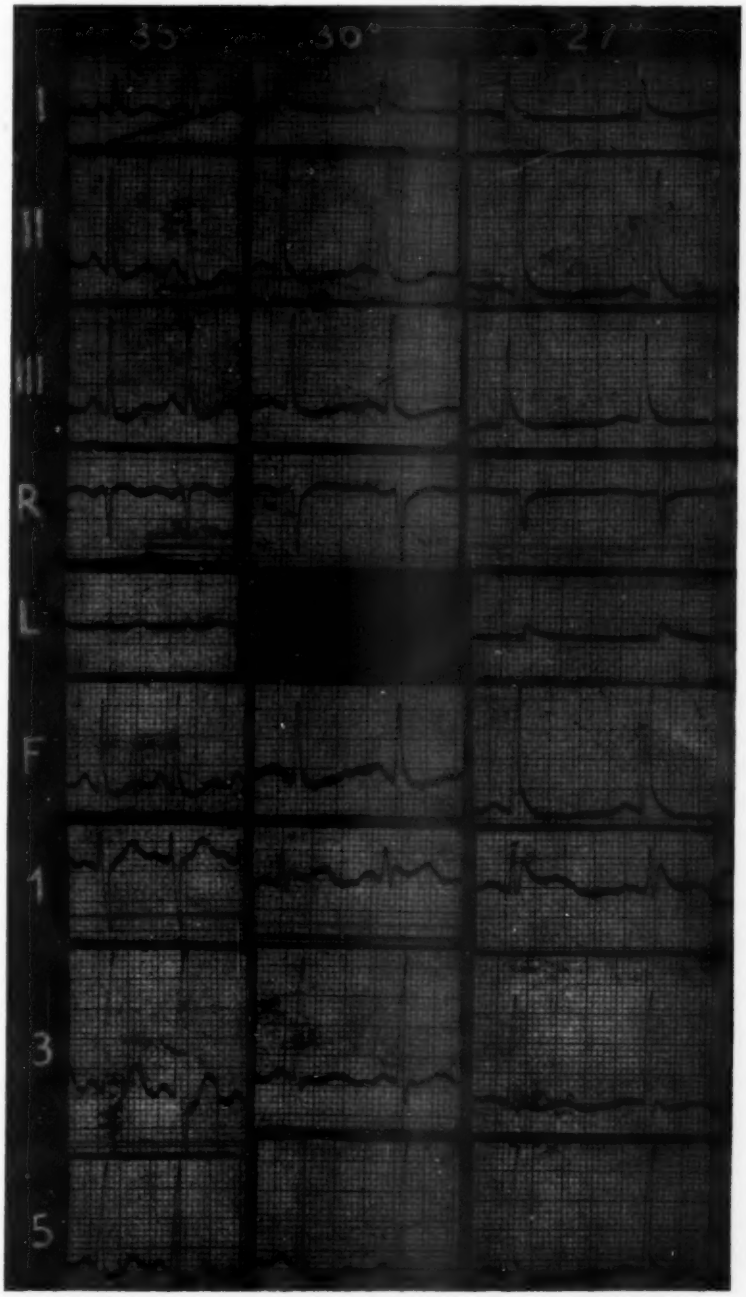

Fig. 11.—35° C.: Sinus tachycardia. Semivertical electrical axis (80 degrees). Depression of the S-T interval in L_{III}, V_3, and V_5. 30° C.: 88 beats per minute. Flattening of the T wave. Incomplete right bundle branch block (V_1). 27° C.: Sinus bradycardia. The flattening of the T wave is general. Complete right bundle branch block. ($Q\text{-}T_c$:0.522 sec.)

habilitation period, but not during undernourishment where the main electrocardiographic changes were an accentuated bradycardia and insignificant modifications of the Q-T $_c$.

The morphologic characteristics of the records obtained in our series of ten patients differ absolutely from those obtained in hypocalcemia. We can thus exclude hypocalcemia, at least as the sole pathogenic mechanism, in our cases. The same may apply to hypopotassemia, only more so, remembering that a clear hyperpotassemia existed in two of our cases.

With respect to the possible comparison of our findings with those observed in advanced undernourishment, it is quite evident that, in spite of the low oxygen consumption determined by hibernation, our patients were not in that situation. With respect to the possible action of the drugs used in the procedure, only in one case was quinidine used, and never procaine amide.

Some actions of the ganglioplegic and neurolythic agents in the genesis of these records cannot be discarded; but the correlation observed between the modifications of the electrocardiogram, especially the prolongation of the Q-T interval and the descent of the body temperature, should be emphasized (Fig. 1 and Table I). The same thing occurs in hypothermia obtained by other methods.[26]

However, it appears clear that the patients hibernated by the Laborit and Huguenard[25] method, present a typical electrocardiographic record—especially below 30° C.—of which the fundamental characteristics are a prolongated Q-T interval and a correlative increase of the area of the T wave.

The fact that, in low temperatures produced with different methods of hypothermia, the risk of ventricular fibrillation exists is widely known, and Churchill-Davidson and associates[11] point out that in order to avoid circulatory complications the temperature should not be allowed to drop below 26° C. However, starting from the hypothesis that pretreatment with ganglioplegic and neurolythic agents would reduce this risk,[41,42] in two of our patients an axillar temperature of 22° C. and 24° C. (23° C. and 25° C. rectal) was obtained, without the least cardiovascular complication. On the contrary, except during the induction period, the electrocardiographic records in general showed, below 28° C., an almost perfect regularity, together with good potentials of all the waves.

On the other hand, in a hibernated patient the sensitivity of the heart to direct stimulus (for example, the introduction of a catheter in its cavities) is not reduced, since we found that the occurrence of arrhythmias in these circumstances does not differ from that found in patients not submitted to artificial hibernation.*

CONCLUSIONS

1. In ten patients electrocardiograms were taken during artificial hibernation. In eight, the records were obtained serially at different temperatures, oscillating between 38° C. and 24° C.

2. In the ten cases the pulse rate increased during the induction period, and in one case it was accompanied by auricular fibrillation.

3. All the patients, once hibernation was stabilized, showed a decrease in

*This problem will be considered in another communication.

the pulse rate (below the normal average and/or the one obtained in basal conditions) together (with a few exceptions) with a prolongation of the P-R and QRS intervals.

4. The Q-T interval was in all patients considerably prolonged. This prolongation was closely related with the descent of the body temperature and concomitantly marked change of the S-T interval occurred.

5. The tendency of the heart to present severe arrhythmias when the temperature fell below 28° C. was not present when the method of neurovegetative disconnection was used together with cold. However, the irritation of the heart's walls produced by catheterization was found to produce arrhythmic phenomena, apparently with the same ease as in nonhibernated patients.

6. The records obtained in artificial hibernation are considered characteristic, even while being, in many aspects, similar in quality to those produced by quinidine and related drugs, and those obtained in extreme malnutrition.

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THE VECTORCARDIOGRAM AND ELECTROCARDIOGRAM IN INTERATRIAL SEPTAL DEFECT

Analysis of 30 Cases

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INTERATRIAL septal defect is the most common single congenital cardiac malformation. Most authors report its occurrence in 7 to 25 per cent of all documented cases of congenital cardiac anomalies.[1-4] Wood and associates[5] found an incidence of 17 per cent in a series of 750 well-authenticated, consecutive cases of congenital heart disease.

It is the purpose of this communication to analyze the electrocardiographic and vectorcardiographic findings in this lesion and to correlate them with right ventricular systolic pressure levels.

MATERIAL AND METHODS

Thirty consecutive patients with interatrial septal defect were selected for this study from the wards and clinics of The Mount Sinai Hospital. Each had been followed for a period of six months to fourteen years. There were fifteen males and fifteen females, ranging in age from 3 to 41 years.

All patients underwent catheterization of the right side of the heart after the initial screening survey, which included obtaining history, physical examination, routine laboratory, fluoroscopic, and radiographic studies. Associated defects within the heart, such as interventricular septal defect and pulmonic valvular stenosis, eliminated the case from inclusion in this series.

Vectorcardiograms were obtained in three plane projections, using the cube reference system of electrode placement.[6] The vector loops were registered either on a Sanborn Viso-Scope or a Technicon Vector-Scope. The three vector component leads were recorded, as was a conventional 12-lead electrocardiogram, with additional right-sided leads in most cases. A direct-writing three-channel Technicon electrocardiograph was employed at a paper speed of 25 or 50 m.m./sec. Standardization employed was 0.5, 1.0, and 1.5 cm. per millivolt.

The electrocardiograms were divided into two main groups: those with an rSR′ pattern in the right precordial leads, and those without it. The rSR′

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records were analyzed for right ventricular hypertrophy and/or right bundle branch block by the criteria of Wilson[7-9] and Barker and Valencia.[10,11] The non-rSR′ group was appraised by the standards of Sokolow and Lyon,[12] and also by using Kossmann's maximum allowable voltages of R and S waves in the precordial leads and ventricular activation times.[13,14] The requisites of Goodwin and Pagnoni[15] for combined hypertrophy in nonrheumatics were also applied to both types of electrocardiograms.

The vector loops were then examined for evidence of right ventricular preponderance, right bundle branch block, and terminal conduction delay. They were classified into the four types previously described.[16-19]

RESULTS

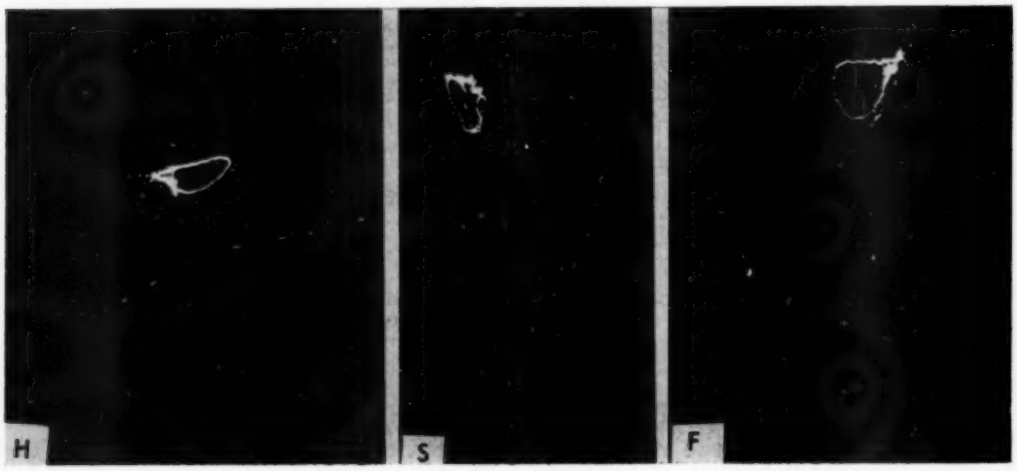
Table I refers to the results of the electrocardiographic evaluation. The rSR′ pattern, present in eighteen of the thirty tracings, was interpreted by the criteria mentioned above, as follows: rSR′ configuration (QRS duration less than 0.08 sec.), 1; complete right bundle branch block, 5; incomplete right bundle branch block, 9; incomplete right bundle branch block with right ventricular hypertrophy, 3.

TABLE I. ELECTROCARDIOGRAPHIC FINDINGS IN THIRTY CASES OF INTERATRIAL SEPTAL DEFECT BASED ON SEVERAL CRITERIA (See Text)

CONFIGURATION		INCOMPLETE R.B.B.B.	COMPLETE R.B.B.B.	INCOMP. R.B.B.B. AND R.V.H.	COMP. R.B.B.B. AND R.V.H.	BIVENTRICULAR HYPERTROPHY	R.V.H.	TOTAL
rSR′	1 (QRS of 0.08 sec. or less)	9	5	3	0	–	0	18
Non-rSR′	1 Normal	–	–	–	–	1	10	12
Total	2	9	5	3	0	1	10	30

Among the remaining twelve non-rSR′ records, ten showed evidence of right ventricular hypertrophy by the criteria of Sokolow and Lyon,[12] while one was electrocardiographically normal. Kossmann's normal voltage values and limits of ventricular activation time were exceeded in only eight of the twelve. One was compatible with the presence of combined ventricular hypertrophy.

Appraisal of the vectorcardiograms revealed right ventricular preponderance in twenty-nine of the thirty cases. Of the thirty vectorcardiograms, fourteen conformed to Type 1 (Fig. 1). The vector forces of this loop, after leaving the isoelectric point or E, are inscribed initially to the right, superiorly and anteriorly for a brief period. The QRS loop then is directed to the left, inferiorly, and somewhat posteriorly. After this early course, the loop turns abruptly in a clockwise direction for the remainder of its inscription. The centripetal limb thus returns to the point of origin, pursuing a path to the right,



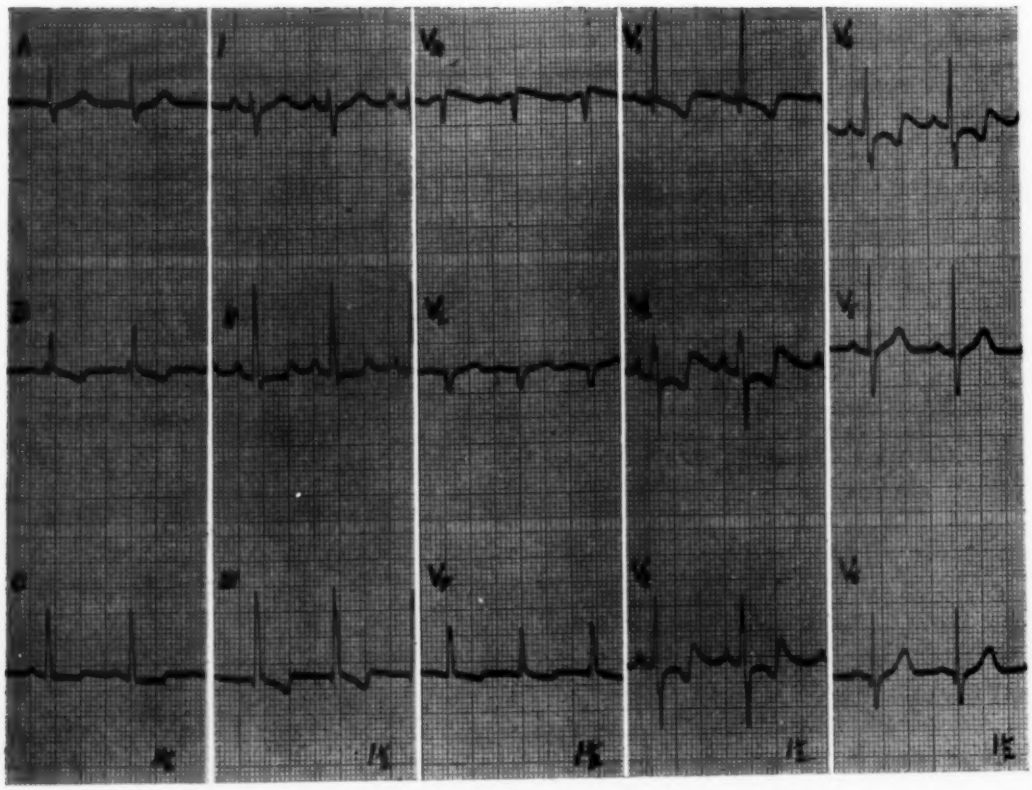
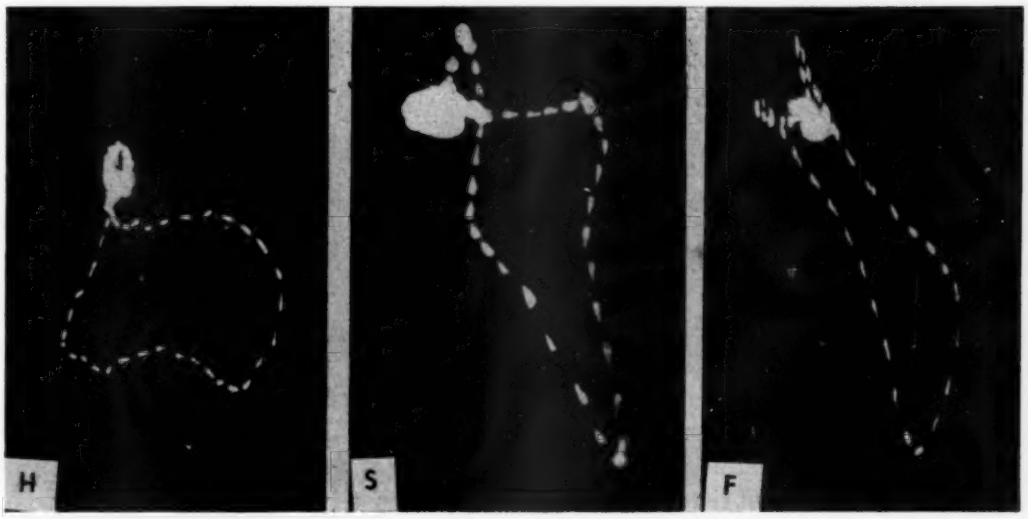


Fig. 1.—Vectorcardiogram of an 8-year-old boy with a right ventricular systolic pressure of 40 mm. It demonstrates right ventricular hypertrophy, Type 1, as described in text. According to the criteria outlined, the electrocardiogram is interpreted as indicative of incomplete right bundle branch block and right ventricular hypertrophy.



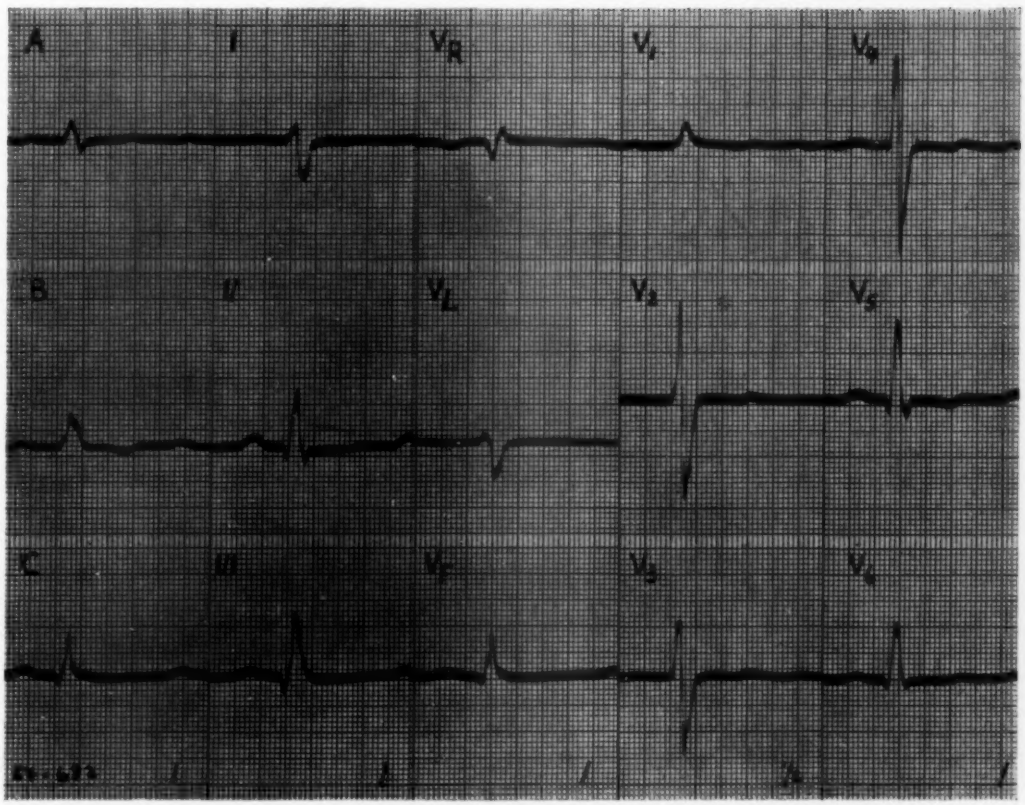


Fig. 2.—The vectorcardiogram of a 29-year-old man whose right ventricular systolic pressure was found to be 40 mm. This is an example of right ventricular hypertrophy, Type 2. The electrocardiogram also displays a right ventricular hypertrophy pattern. Note the tall R in V_1.

superiorly, and anteriorly in relation to the centrifugal or afferent segment. Electrocardiograms derived from this type of loop (Fig. 1) are predominantly of the rSR′ variety.

There were four Type 2 spatial loops (Fig. 2) which were also clockwise in direction of inscription. The distinguishing characteristic was their considerably shorter initial course to the left and the more right and anterior orientation of the major portion of the vector forces. This configuration results essentially in a tall, often notched R wave in V_1 (Fig. 2). Two vectorcardiograms of bizarre form constitute Type 3 (Fig. 3). In addition to the three groups described above, there were nine records of right ventricular preponderance, which also showed marked slowing in the terminal part of the loop, as evidenced by the closer apposition of the time markings. This vector configuration, which is classified as Type 4, assumes an unusually superior orientation, as seen in the sagittal and frontal plane projections[19] (Fig. 4).

There was no consistent relationship between the Type 4 QRS loops with terminal conduction delay and the duration of the QRS complex in the derived electrocardiograms. There were three electrocardiograms in this category with complete right bundle branch block, three with incomplete right bundle branch block, two with right ventricular hypertrophy, and one record within normal limits.

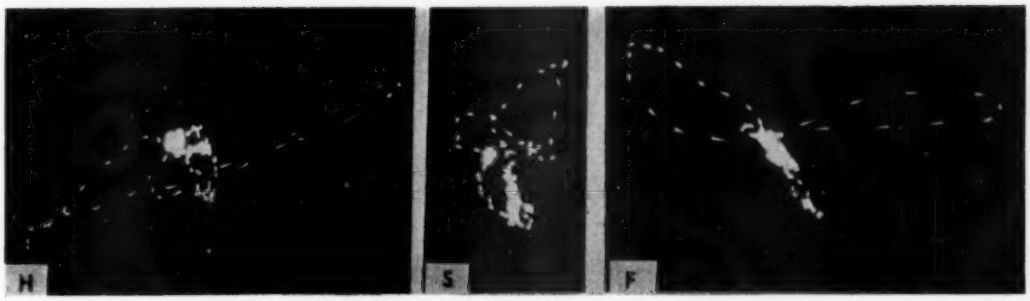
There appeared to be a somewhat lower average right ventricular systolic pressure in the rSR′ group (41 mm. Hg) than in the other (52.5 mm. Hg). The range of pressures in each, however, was essentially the same; 25 to 85 mm. Hg in the former, as compared to 30 to 89 mm. Hg in the non-rSR′ class (Table II).

TABLE II. RELATION OF RIGHT VENTRICULAR SYSTOLIC PRESSURE TO ELECTROCARDIOGRAPHIC AND VECTORCARDIOGRAPHIC TYPES

TYPE	rSR′	NON-rSR′	TYPE 1 LOOP	TYPE 2 LOOP	TYPE 3 LOOP	TYPE 4 LOOP
	18	12	14	4	2	9
Right ventricular systolic pressure (mm. Hg)	range of 25-85; average 41	range of 30-89; average 52.5	average 35	average 52	average 38	average 45

There was no well-delineated relation between vector loop types and pressure levels (Table II). The average right ventricular systolic pressure in Type 1 was 35 mm. Hg; in Type 2, it was 52 mm. Hg; Type 3, 38 mm. Hg; and Type 4, 45 mm. Hg.

Among the rSR′ tracings, there were twelve patients with right axis deviation, two with left axis deviation, and four with a normal axis. In the electrocardiograms not exhibiting rSR′, there were seven instances of right axis deviation and five with left. The average right ventricular pressure in the cases with left axis deviation was 48.4 mm. Hg (range of 38 to 85 mm. Hg); in the right axis deviation group it was 41.6 mm. Hg (range of 28 to 82 mm. Hg).



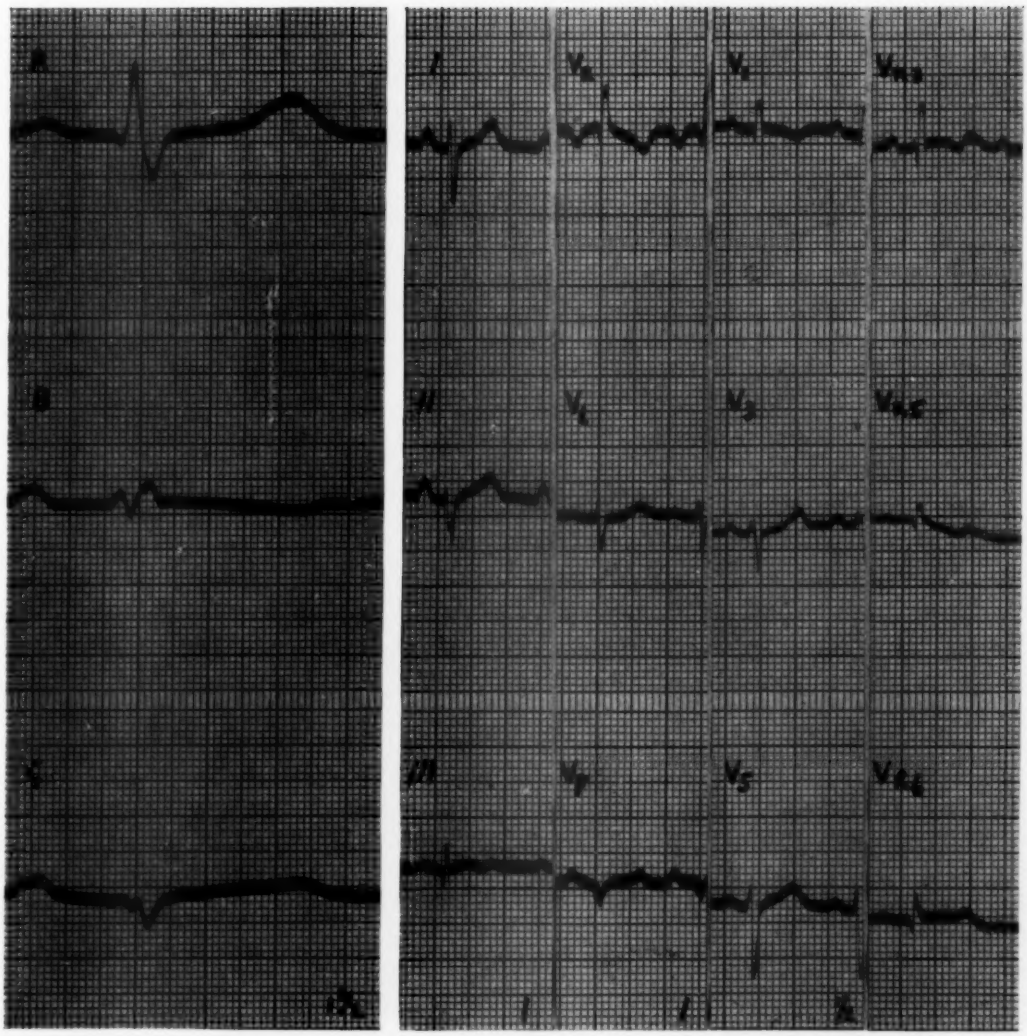
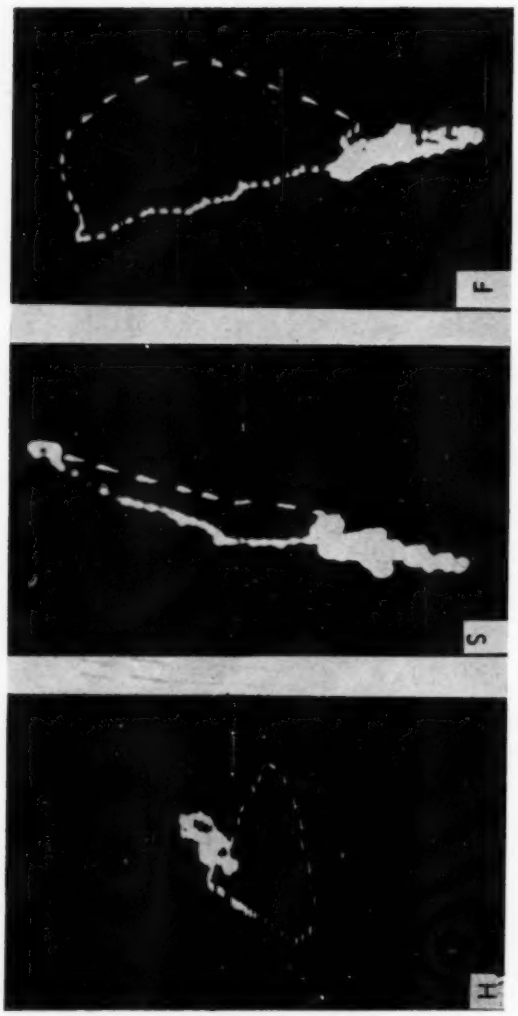


Fig. 3.—The vectorcardiogram of a 4-year-old boy. Right ventricular systolic pressure was 46 mm. It represents the bizarre Type 3 variety of right ventricular hypertrophy. The electrocardiogram reveals incomplete right bundle branch block.



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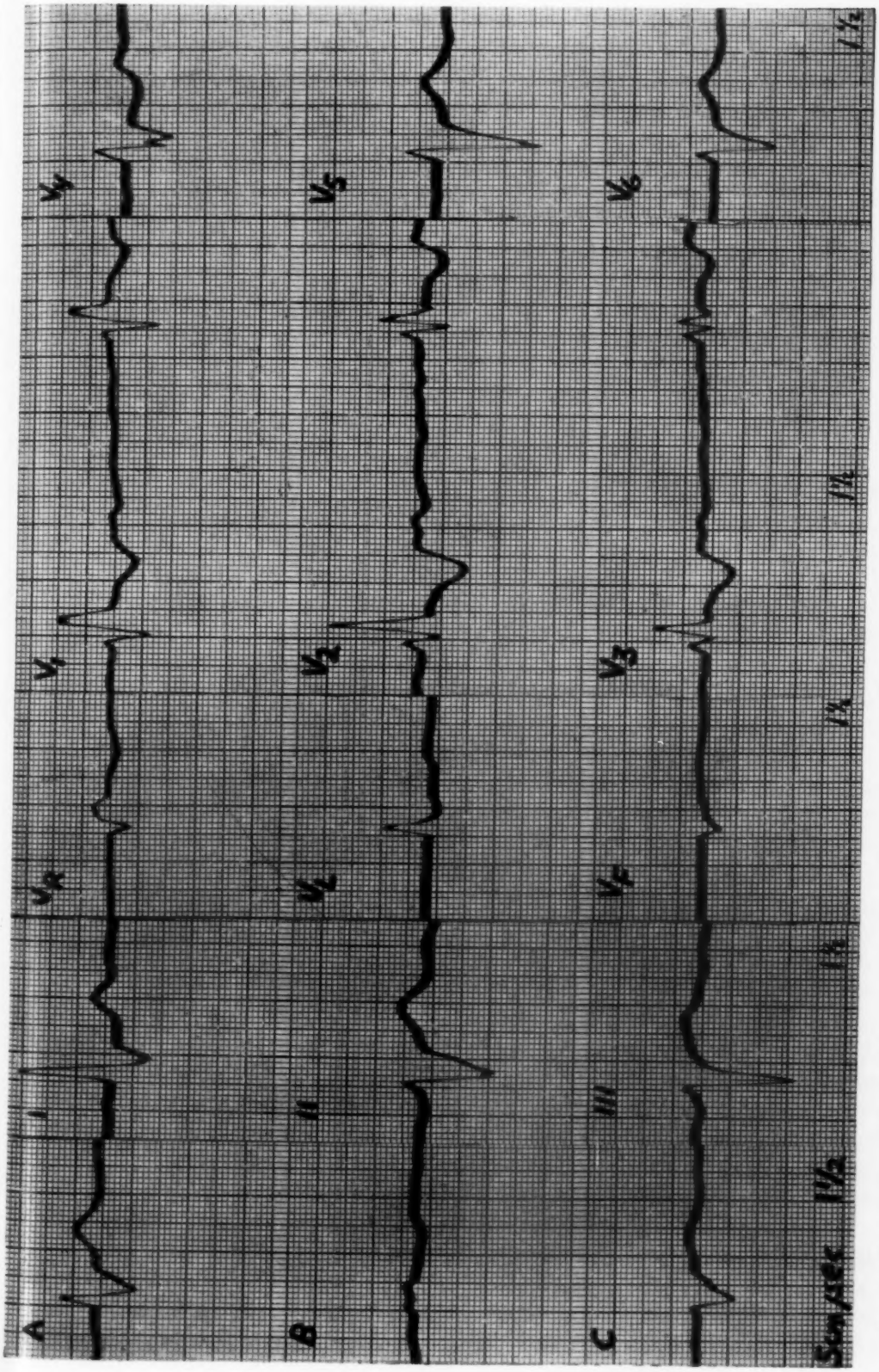

Fig. 4.—Vectorcardiogram of a 35-year-old woman with a right ventricular systolic pressure of 85 mm. This is classified as a member of the Type 4 right ventricular hypertrophy group. The electrocardiogram shows complete right bundle branch block.

The correlative analysis is limited to the intracardiac pressures, although we realize that this is not the only important factor. Cardiac work would actually be the more significant correlate, since in interatrial septal defect considerable increase of cardiac output often exists without appreciable changes of right ventricular pressure.

DISCUSSION

Interatrial septal defect is known anatomically to be associated with right ventricular hypertrophy and dilatation. This is, in part, due to the abnormal shunt of blood from the left to the right side of the heart and also to a congenital factor, independent of the hemodynamic alterations.[20-25] The fact that the basic configuration of right atrial and ventricular enlargement and hypertrophy, associated with a large pulmonary artery, is found at birth is of interest. An interatrial septal defect is so akin to the physiologic communication existing during fetal life that appreciable effects should not be expected dynamically. Unequal development in utero of the two sides of the heart must then be considered, in good part, responsible for the right-sided preponderance. The major shunt occurs from left to right, because the left atrial pressure is greater than the right. This results in a right ventricular output almost twice that of the left ventricle, or more.[26-30] In addition to the right-sided enlargement, marked dilatation of the pulmonary artery and its branches and some degree of hypoplasia of the left ventricle are also seen.[1,4,20-25]

These consistent anatomic observations provide a means of studying the vectorcardiographic and electrocardiographic patterns associated with unilateral right ventricular hypertrophy.[14]

Eighteen of our thirty cases revealed an rSR′ pattern. This configuration, which may occur anywhere in the right-sided precordial leads, consists of an initial r or R wave, followed by a deflection below the base line of varying depth (s or S wave) and a late, wide, and usually slurred r′ or R′. The early r wave may be minute, or even isoelectric. In this instance, V_1 will present a qR complex. The isoelectricity of the r can be conclusively demonstrated by simultaneously registering other precordial leads.[31,32] The duration of the r wave usually varies from 0.01 to 0.03 second. The S wave may be deep or shallow. We found the duration of the QRS to range from 0.06 to 0.15 second. The T wave associated with the rSR′ was usually diphasic or inverted.

This particular configuration in the right precordial leads has long been observed in association with interatrial septal defect.[33] Earlier observers thought it to be pathognomonic, reporting its incidence as high as 80 to 90 per cent.[34,35] It is generally agreed, however, that the occurrence of the rSR′ is not frequent enough to regard it as a sine quo non for the diagnosis of this lesion. As many as one-third of the cases will be missed if it is so regarded.[36]

Many theories have been postulated as to the mechanism of rSR′ production in interatrial septal defects. Gros, Gordon, and Miller[37] believe that it is a physiologic pattern in the first week of life, but that it is suggestive of right heart strain beyond that period. According to Donzelot and associates,[38] there are three types of electrocardiographic right heart strain patterns, each re-

flecting a different pathophysiologic phenomenon. These are the "adaptation," "surcharge," and "barrage" forms. The "adaptation" pattern represents the mildest form of strain and is seen in such lesions as the tetralogy of Fallot. The "surcharge" type, allegedly indicating an intermediate level of right heart strain, is characterized by an rSR′ complex in the right precordial leads and is to be expected in cases of interatrial septal defect. There is considerable support for this concept.[35,39,40] The tall R wave and inverted T waves of the "barrage" type in the right chest leads are frequently described in association with the markedly elevated right ventricular systolic patterns seen in cases of pulmonic valvular stenosis with intact interventricular septum and normal aortic root.[41,42] This electrocardiographic pattern, however, can occur in the absence of a marked pressure increase.[43] It is apparent from the foregoing that many studies reveal a broad relationship of right ventricular pressure levels to right precordial patterns. The tall, notched R wave seems to occur in the presence of higher right ventricular pressures than does the rSR′ configuration. This observation cannot, however, be applied to any particular case with assurance. There are many exceptions in our own series. While Donzelot's concept of the rSR′ reflecting a "surcharge" pattern in interatrial septal defect is an attractive one, it applied in only eighteen of thirty proved instances in this study. It appears, therefore, that there is no consistent relationship between electrocardiographic configuration and right ventricular pressure levels.

Cabrera[45-47] describes two types of ventricular overloading: systolic and diastolic. Systolic overloading, as in pulmonic stenosis, is said to produce the tall, notched R wave and the negative, symmetrical T wave in the right precordial leads. Diastolic overloading of the right ventricle, characterized by the imposition of a large volume of blood in the chamber, as in interatrial septal defect, presumably produces the pattern of incomplete or complete right bundle branch block. Ten of our thirty patients presented a "systolic overloading" pattern in the presence of interatrial septal defect alone. Other studies here and elsewhere[43,44] have revealed instances of the "diastolic overloading" pattern in isolated pulmonic valvular stenosis.

Investigation following cardiac surgery has yielded additional information. In a recent series of thirty-two patients with interatrial septal defect, in which direct closure of the ostium secundum was effected by the open heart technique, Blount and associates[48] found a significant decrease in pulmonary artery pressure in each case. This was accompanied by a notable degree of regression of the rSR′ pattern toward normal, as evidenced by a considerable decrease in the amplitude of the secondary R wave in Lead V_1. In addition, a completely normal right precordial lead configuration evolved in three patients. In other series of cases of isolated pulmonic stenosis or interatrial septal defect,[36,49] in which the electrocardiograms preoperatively revealed tall, notched R waves in V_1, there often developed an rSR′ pattern after successful operation. This seems to suggest that the rSR′ complex in patients with congenital heart disease usually does not reflect a conduction disturbance, but rather a form of moderate right ventricular preponderance.

Axis deviation is still regarded by some as a significant index of right ventricular pressure elevation.[33,36,39] Our own observations do not permit our support of this. In this series, the right ventricular pressure range was similar in both the right and left axis deviation groups. Application of the principles of vectorcardiography suggests that there is no real basis for regarding axis deviation as of significance in right ventricular preponderance.[17]

This study demonstrates that the vectrocardiogram is of considerable aid in detecting the presence of right ventricular preponderance, as has been cited by others.[18,44,50] The single vectorcardiogram which failed to indicate diagnostically this change was, nevertheless, abnormal and bizarre. The increased accuracy of the vectorcardiogram in the diagnosis of right ventricular preponderance is not unexpected. The vectrocardiogram provides the instantaneous computation of the phase relationship of voltages as recorded on a Cartesian reference system.[6] The direction of inscription and shape of the vectorcardiographic curve permits immediate visual analysis of the phase relationship of voltages. This information is not available from individually recorded electrocardiographic leads and can be extracted only with much difficulty from simultaneously registered component leads of the vector reference system.

The significance of the terminal slowing in the spatial QRS loop of Type 4 has been investigated.[19] Experiments during which the electrocardiogram and right ventricular pressure pulse were simultaneously recorded reveal that there is a delay in the electrical-mechanical interval (onset of QRS to beginning of rise in right ventricular pulse). Other instances in this study of vector loops, displaying right ventricular hypertrophy without conduction delay and rSR′ in the right-sided precordial leads, showed no delay in right ventricular contraction. Thus, by physiologic experiment, it has been shown that the presence of conduction delay in a vectorcardiogram demonstrating right ventricular preponderance is significant. It has also been shown that the rSR′ pattern does not necessarily indicate conduction disturbance. This strongly suggests that this electrocardiographic configuration should no longer be considered a pattern of "incomplete right bundle branch block." In the majority of cases of congenital heart disease in which it is present, it is most often an indication of right ventricular hypertrophy rather than bundle branch block.

It is interesting that one of these examples of pure interatrial septal defect should have fulfilled the electrocardiographic criteria of combined ventricular hypertrophy. This appears to represent a false positive.

The criteria of Sokolow and Lyon for right ventricular hypertrophy, as applied to the non-rSR′ group, was effective in diagnosing ten of twelve cases, while the more rigid standards of Kossmann detected only eight. The former criteria, though appearing to be more reliable in their ability to indicate right ventricular preponderance, have been shown in other studies to include a considerable number of normal subjects when applied to a heterogeneous group.[14] This high incidence of false positives is due to the modest voltage values. Conversely, though electrocardiograms exceeding Kossmann's normal voltage values are truly instances of right ventricular hypertrophy, his standards are so strict as to overlook its presence in some cases. False positive diagnoses, however, will not occur.

SUMMARY

1. Thirty consecutive, well-authenticated cases of interatrial septal defect have been studied vectorcardiographically and electrocardiographically.

2. An rSR′ configuration was present in eighteen of the thirty cases.

3. The electrocardiogram, applying the criteria described, detected the presence of right ventricular preponderance in thirteen of the thirty patients.

4. The vectorcardiogram demonstrated right ventricular preponderance in twenty-nine of thirty cases.

5. Four types of spatial QRS loops characteristic of right ventricular preponderance are described, including Type 4 with terminal conduction delay.

6. There is no consistent relationship in this study between right ventricular pressures and electrocardiographic or vectorcardiographic patterns, though rSR′ configurations were found to have a lower average systolic pressure than the non-rSR′ group.

7. The theories of the pathophysiologic significance of the rSR′ are reviewed. Most investigators believe that the tall R in V_1 reflects higher ventricular pressures than does the rSR′, but there are many exceptions to this observation.

8. Axis deviation does not appear to be a reliable index of the degree of right ventricular hypertrophy, nor does it vary consistently with changing ventricular systolic pressures.

Cardiac catheterizations were performed by the Cardiac Catheterization Group under the direction of Dr. Alvin Gordon. The technical assistance of Miss Ruth Jaspan is appreciated.

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THREE PATIENTS WITH CONGENITAL PULMONIC VALVULAR STENOSIS SURVIVING FOR MORE THAN FIFTY-SEVEN YEARS

Medical Histories and Physiologic Data

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THE recent rapid development of surgical procedures which permit not only safe attack on valve lesions in the heart, but also in many instances their mechanical restoration toward normal, has placed the clinician in the embarrassing position of not knowing enough about the natural history of certain congenital lesions. Of course, it was recognized long ago that patients with congenital heart lesions producing cyanosis rarely lived far into adult life. Until recent years, however, precise diagnosis was looked upon as an unnecessary academic exercise.

Since it has been difficult to maintain control series of patients in conditions where operations appear so logical and seem to offer definite improvement, we have thought it worth while to record observations on three patients of advanced age who had stenosis of the pulmonary valve. The natural history of this lesion, when occurring singly, is shrouded in a good deal of mystery, which adds to the difficulty of selecting patients for surgical correction of the abnormality. Other things being the same, patients with severe lesions die young; whereas those with mild lesions have an excellent prognosis. Between these two extremes the majority of the patients are found, and the problem is how to select those whose life is jeopardized by the lesions and leave untouched those who might well live to a ripe old age without surgical attack. The three selected patients presented here throw some light on the problem of pulmonary stenosis in middle years or beyond.

CASE REPORTS

Case 1.—F. Z., a white man, 69 years old, was admitted to the University of Iowa Hospitals on Dec. 2, 1954, with complaints of shortness of breath and swelling of the ankles. His health had been excellent, and he had worked hard and steadily as a farm hand and laborer prior to the

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TABLE I. HEMODYNAMIC DATA* FROM THREE SENESCENT PATIENTS WITH PULMONIC VALVULAR STENOSIS

PATIENT	AGE	CARDIAC CATHETER SIZE (FRENCH NO.)	CARDIAC INDEX† (L./MIN./M.²)	RIGHT VENTRICULAR PHASIC PRESSURE (MM. HG)	PULMONARY ARTERY		OCCLUDED DISTAL BRANCH OF PULMONARY ARTERY MEAN‡ PRESSURE (MM. HG)	SYSTEMIC ARTERY	
					PHASIC PRESSURE (MM. HG)	MEAN‡ PRESSURE (MM. HG)		PHASIC PRESSURE (MM. HG)	MEAN‡ PRESSURE (MM. HG)
F.Z.	70	9	—	75/0 (5)	34/14	19	15	175/95	120
M.C.	57	7	3.1	105/0 (10)	24/9	16	—	140/75	100
D.L.	57	8	3.9	67/0 (10)	22/12	17	10	130/85	105

The observations of blood pressure levels during cardiac catheterization studies are summarized in this table. The end-diastolic pressure in the right ventricle is recorded in parentheses. F. Z. had symptoms and signs of mild left ventricular decompensation at the time of catheterization, as indicated by the reflected left atrial and pulmonary capillary mean pressure level of 15 mm. Hg.

*Registered with a Sanborn electromanometer and direct-writing biophysical recorder.

†Determined by the Fick principle.

‡Electrically integrated.

onset of his symptoms in 1953. The illness began in July of that year with an attack of precordial distress. This attack took place while he was chopping wood, and it consisted of sudden severe "tightness in the chest" and difficulty in breathing. There was no chest pain. He subsequently developed persistent exertional dyspnea, orthopnea, and ankle edema. In spite of careful questioning, no antecedent history of cardiovascular disease could be elicited. Urinary symptoms of hesitancy, some incontinence, urgency, and pain on micturition made their appearance one week before admission.

Findings.—Although obviously ill, the patient was normally developed and muscular. This appearance tended to confirm the history of previous excellent health. The blood pressure was 180/120 mm. Hg and the heart beat was regular at 72 per minute. The brachial and radial arteries were thickened and tortuous. The mean level of pulsation in the external jugular veins was just above the sternal angle, when the patient was in a semirecumbent position. Compression of the right upper quadrant of the abdomen caused this pressure to rise significantly. The liver edge was 6 cm. below the right costal margin, and posttussive, moist, inspiratory râles were heard over both lung bases. The apex beat was in the fifth left intercostal space inside the midclavicular line; from here to the sternum a diffuse, forceful cardiac impulse was visible and palpable. A systolic thrill was felt over the upper part of the sternum and the adjacent left precordium. It was most intense over the left second rib near the sternum. The first heart sound was clearly split. Both components were heard easily along the sternal borders, but only the first was audible at the apex. The second component was louder than the first in the pulmonic area of the precordium. The second heart sound was split also, but the second component was diminished in intensity despite the presence of pulmonary edema. A long Grade 3 systolic murmur was heard over most of the left anterior chest. It was harsh in quality in the aortic and pulmonic areas, but high pitched and whistling along the lower left sternal border. A high-pitched early diastolic murmur was heard best in the left third and fourth intercostal spaces adjacent to the sternum.

Four electrocardiograms recorded between Dec. 3, 1954, and Jan. 2, 1955, were essentially the same. They were characterized by S-T-segment depression in Leads I, II, III, aV_F, and V_4 through V_6. Sharp T-wave inversions also were present in Leads I, aV_L, and V_4 through V_6. In Lead V_6 the time from the onset to the peak of the R deflection was 0.04 second. This was interpreted as indicating myocardial damage. There was no sign of right ventricular hypertrophy (Fig. 1).

Cardiac fluoroscopy showed evidence of pulmonary emphysema and a very prominent pulmonary artery which pulsated markedly. There was a slight "hilar dance" but the peripheral vascular pattern was less well marked than normally. The aortic knob and innominate artery were prominent and showed an increased amplitude of pulsation. The esophagus was indented by the aorta, the pulmonary artery, and the left atrium. In the left anterior oblique projection the right ventricle appeared greatly enlarged and the left only slightly enlarged. No calcification was seen. Roentgenograms (Fig. 2) confirmed some of the fluoroscopic observations.

A variety of unusual diagnoses was entertained. The radiographic findings were compatible with a patent ductus arteriosus. Pulmonary hypertension on the basis of emphysema was considered as another possibility. Although some form of congenital heart disease seemed most likely, we did not think of pulmonary valve stenosis. The presence of pulmonary emphysema certainly added to the diagnsotic difficulties. The problem was resolved during cardiac catheterization when a sharp systolic pressure gradient (Table I) was found to exist between the right ventricle and the pulmonary artery. There was no evidence of a shunt of blood into the great veins, the right side of heart, the pulmonary arteries, or the systemic vessels. Thus, the only demonstrable lesion was pulmonary stenosis. The elevated pressure recorded from the distal pulmonary artery occlusive position was thought to be due to left ventricular decompensation, causing pulmonary capillary congestion. The cause of the high-pitched early diastolic murmur was presumed to be mild aortic regurgitation associated with left ventricular dilatation of a degree insufficient to produce diagnostic changes in the systemic arterial pressure pulse tracings.

Clinical Course.—Routine treatment for congestive heart failure, including digitalization, was followed by rapid and steady improvement. The physical signs of cardiac enlargement disappeared and the patient was discharged from the hospital on Jan. 5, 1955. Two weeks later he developed severe orthopnea, paroxysmal nocturnal dyspnea, and peripheral edema. He was

readmitted on Feb. 16, 1955, and responded well to additional hospital treatment. One week later he passed grossly bloody urine for the first time. Urogenital examination revealed nodularity in the right lobe of the prostate and an osteoclastic lesion in the left ilium. Transurethral resection of adenocarcinomatous prostatic tissue and, later, bilateral orchidectomy were carried out under spinal anesthesia. After a short and uneventful convalescence he was discharged from the hospital in good condition. However, he soon discontinued his digitalis, and pulmonary symptoms and widespread peripheral edema returned. Treatment was effective once again. He was seen in July, 1955, and was found to be maintaining myocardial compensation. Nevertheless, edema and dyspnea reappeared in August, 1955, and responded only temporarily to treatment. The patient died in October, 1955, in intractable congestive heart failure. Request for autopsy was denied. Pulmonary valvuloplasty never was offered to this patient because of the poor state of his myocardium and the mild degree of his valvular stenosis.

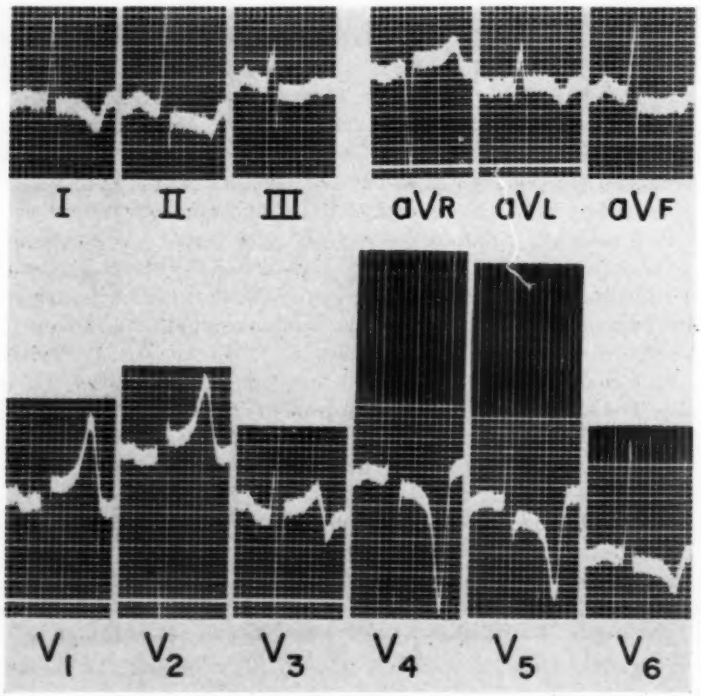
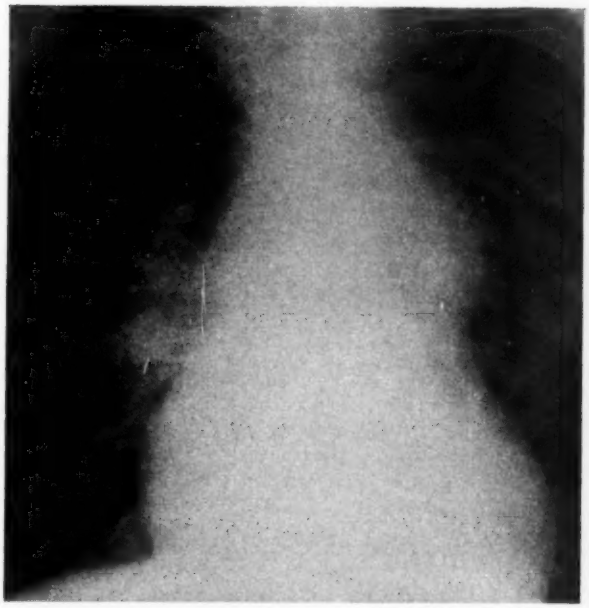


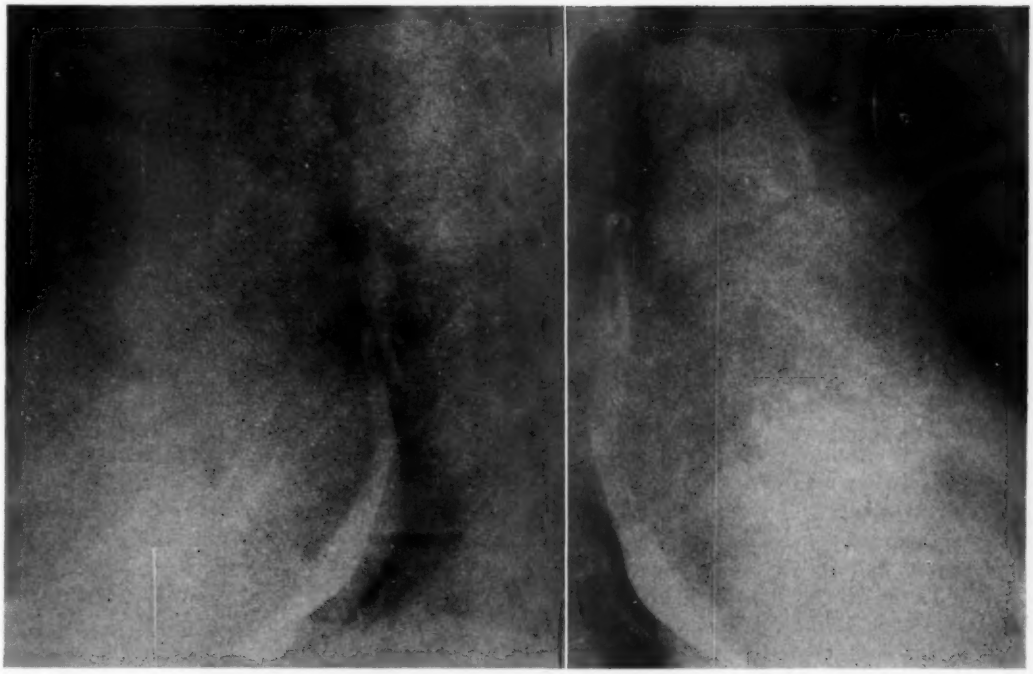
Fig. 1.—Electrocardiogram of F. Z. recorded before he had been given any digitalis preparation None had been recorded before he suffered from a coronary thrombosis. There is no evidence of right ventricular hypertrophy. Inverted T waves and depressed S-T segments in the so-called "left ventricular complexes" are shown well.

CASE 2.—M. C. is a 57-year-old white woman who reported to the Medical Clinic on Feb. 2, 1955, with a written list of complaints. This included weakness, dizziness, vomiting, nervousness, faintness, chronic nonproductive cough, chest pain, occasional shoulder pain, and pain in the hips and knees. All of these were old complaints and previous observation in the hospital had failed to reveal causes for them. Her previous hospital records contained diagnoses of chronic cholecystitis and endometrial hyperplasia; a diagnosis of "acyanotic congenital heart disease" had been made in 1947. In spite of her many chronic complaints, she had worked intermittently as a housekeeper and laundress. Careful questioning and examination of the previous hospital records failed to reveal evidence of physical disability.

Findings.—Her appearance was that of a short, obese white woman with sighing respiration. She did not appear ill and was not cyanotic. Her blood pressure was 140/80 mm. Hg and the heart beat was regular at 72 per minute. There were no physical signs of heart failure or cardiac enlargement. The first heart sound was not unusual. The second element of the split-second



A.



B. *C.*

Fig. 2.—*A*, Posteroanterior chest film. Note the considerably enlarged pulmonary artery segment, the enlarged right branch, and the diminished peripheral vascular pattern. *B* and *C*, LAO and RAO projections, respectively. These demonstrate the right and left ventricular hypertrophy and the enlarged pulmonary artery trunk.

heart sound heard in the pulmonic area was thought to be diminished in intensity. A long, harsh, Grade 4 systolic murmur was heard over most of the chest and in the neck. It was loudest in the second and third left intercostal spaces near the sternum. The electrocardiogram (Fig. 3) was interpreted as showing incomplete right bundle branch block and right ventricular hypertrophy.

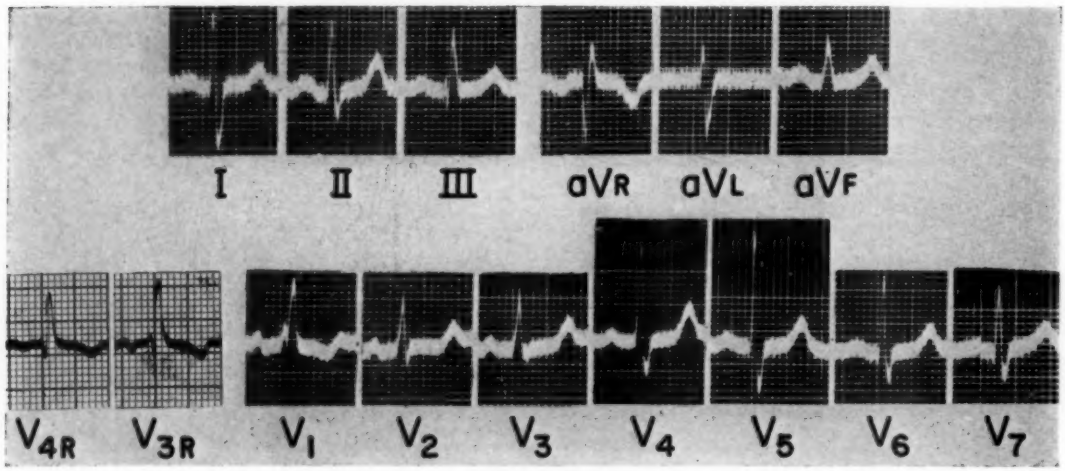


Fig. 3.—This electrocardiogram is interpreted as showing incomplete right bundle branch block and right ventricular hypertrophy.

The obesity, the habitus, and the relatively high position of the diaphragm made fluoroscopic evaluation of the peripheral pulmonary vascular markings somewhat difficult. However, it was felt that these markings were actually normal or diminished in size. The pulmonary artery segment was greatly enlarged and exhibited increased amplitude of pulsations. There was moderate right, but no left ventricular enlargement. Except for indentation of the esophagus by the enlarged pulmonary artery, no abnormalities were noted during the barium swallow. The fluoroscopist made a tentative diagnosis of pulmonic valvular stenosis on the basis of his findings. Two roentgenograms of the chest (Fig. 4) taken 15 years apart showed little if any change in the cardiac silhouette. Cardiac catheterization revealed a marked systolic pressure gradient (Table I) between the right ventricle and the pulmonary artery. Again there was no evidence of a shunt.

Clinical Course.—No objective evidence of disability was found during ten days of hospital observation. Although the patient's complaints continued, she was active about the ward and often helped the nurses in the care of other patients. Pulmonary valvuloplasty was not recommended, and the patient was discharged. She returned in March, 1955, and all findings were essentially the same.

CASE 3.—D. L., a 57-year-old white man, was admitted to the hospital on June 1, 1955, because of recurrent attacks of chest pain. The first hint of illness had been in 1932, when he suddenly lost consciousness while stooping to repair an automobile headlight. There were apparently no premonitory symptoms and unconsciousness lasted for only a few seconds. He neither had a convulsion nor became cyanotic. His physician discovered a heart murmur and advised him to limit his physical activity. The murmur became audible to the patient after attention had been directed to the heart. His wife also could hear the bruit from a distance of several feet. Following this attack of unconsciousness there were two years of relatively little physical activity. During this time the patient experienced several episodes of momentary impairment of consciousness and observed that complete recovery from each of these required three to four minutes of rest. In 1934 he returned to work as an automobile mechanic and was free from symptoms for the next seventeen years, except for one other similar attack of unconsciousness in 1942. During these years he worked regularly at occupations which often required rather strenuous physical exertion. The heart murmur became inaudible to both the patient and his wife in 1946. There were no events in the history to account for its disappearance.

A.

B.

Fig. 4.—*A*, Posteroanterior chest film taken in 1940. *B*, Posteroanterior chest film, 1955. Both show the enlarged pulmonary artery and the normal or minimally diminished peripheral vascular pattern. There has been no apparent progression in the abnormality in fifteen years.

In 1951 the patient again lost consciousness for a few seconds. This occurred on standing after working beneath an automobile. As consciousness returned he experienced dyspnea and severe, sharp, twisting pain under the left nipple. The pain persisted for four or five days and was made worse by deep breathing or coughing. After six months of rest he returned to work as a drill-press operator and worked regularly until May, 1954, when he again had an attack of impaired consciousness, which was relieved by a few minutes of rest. During the year prior to admission, attacks of left upper precordial pain were produced regularly by strenuous exertion or anxiety. These were relieved in fifteen minutes by rest but were not relieved by nitroglycerin.

Findings.—The patient was normally developed and did not appear ill. His blood pressure was 130/85 mm. Hg, and the heart beat was regular at 88 per minute. There were no physical signs of heart failure or cardiac enlargement. The first heart sound was split and was loudest just to the left of the sternum in the second intercostal space. The first element of the split sound was louder at the apex, while the second element was louder at the base. The second heart sound was minimally split. There was a Grade 3 systolic murmur, loudest in the third left intercostal space. No other significant physical signs were observed. The electrocardiogram (Fig. 5) was interpreted as showing evidence of right ventricular hypertrophy. A tentative diagnosis of pulmonary stenosis was made on the basis of these physical and electrocardiographic findings.

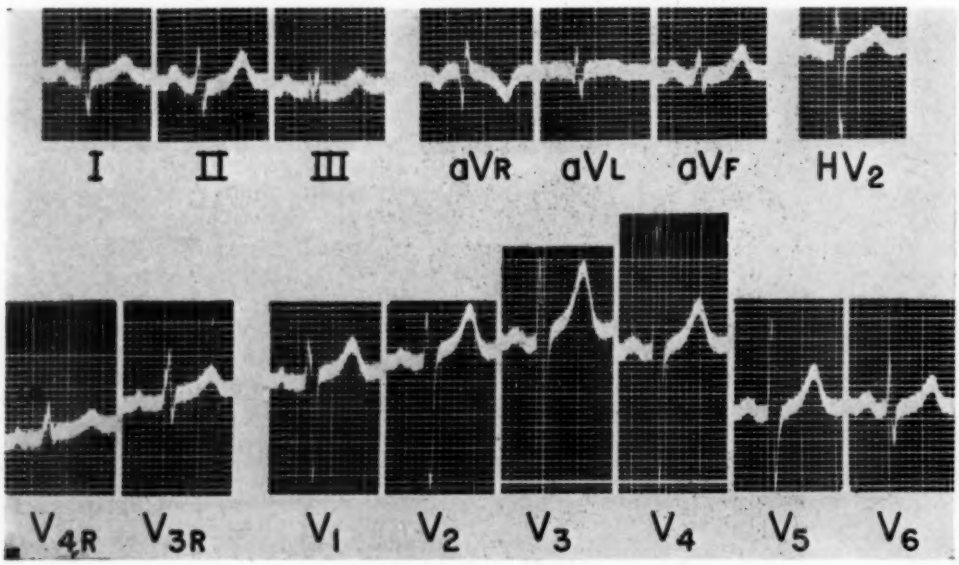
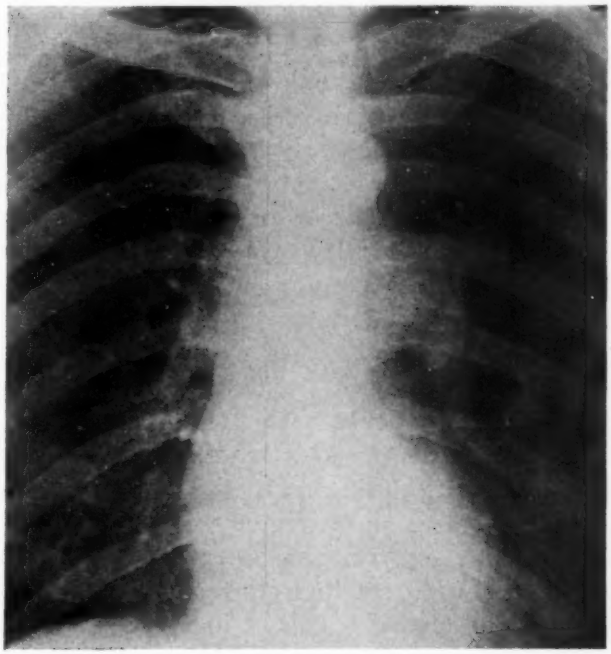
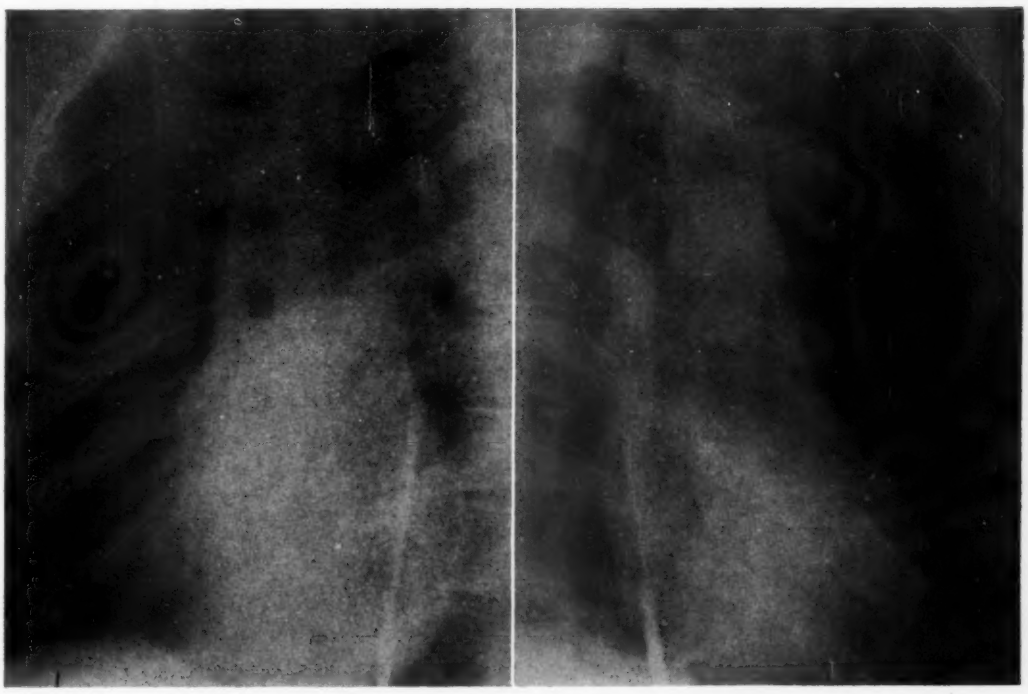


Fig. 5.—This electrocardiogram is interpreted as showing evidence of right ventricular hypertrophy: the activation time in Lead V_{4R} is .04 second.

Fluoroscopic examination of the heart revealed a normal or slightly prominent aortic knob. The pulmonary artery segment was enlarged and showed increased amplitude of pulsations without evidence of a left-to-right shunt. No left atrial enlargement was observed during the barium swallow. Slight right ventricular enlargement was seen in the left anterior oblique projection. There was no evidence of left ventricular enlargement. Roentgenograms (Fig. 6) tended to confirm these fluoroscopic findings. Idiopathic dilatation of the pulmonary artery was considered as a possible diagnosis. Again the problem was resolved when cardiac catheterization disclosed a marked systolic pressure gradient between the right ventricle and the pulmonary artery (Table I), confirming the diagnosis of pulmonary stenosis. There was no evidence of a left-to-right or a right-to-left shunt of blood in the heart or between the great vessels. This patient likewise was discharged without a recommendation for pulmonary valvuloplasty.



A.



B. *C.*

Fig. 6.—*A*, Posteroanterior chest film. Note the enlarged pulmonary artery and the enlarged left branch, as well as the normal or diminished size of the right branch and the peripheral vascular pattern. *B* and *C*, LAO and RAO projections, respectively. These demonstrate the enlarged pulmonary artery and the right ventricular hypertrophy.

DISCUSSION

The clinical courses lead us to believe that the first and second patients were very little disturbed by their valve lesions. F.Z. was without symptoms until he had what seems almost certainly to have been a myocardial infarction at the age of 69. M.C. had a variety of symptoms, but no objective evidence of disability. D.L. had two episodes of loss of consciousness and several short periods of impaired consciousness. These may have been caused by the impediment to blood flow produced by his pulmonic stenosis. At present he is having episodes of pain in the chest precipitated by great exertion or by worry. The cause of this pain has not been established with certainty. It differs from that described by Lowance and associates,[1] and Hillman,[2] who mention chest pain as a terminal symptom in patients with pulmonic stenosis. Abrahams and Wood[3] have observed two patients with retrosternal pain on exertion.

Two of our three patients had a clearly split first heart sound. The second element was loud and snapping in the region of the left second intercostal space near the sternum. This is a sign we have observed in many patients with pulmonic stenosis. We believe it results from tensing of the cone-shaped stenotic pulmonary valve early in systole. This is in agreement with Rheinhold and Nadas'[4] observation of accentuation of the semilunar component of the first heart sound in some patients with mild pulmonic stenosis. Leatham[5] and Leatham and Vogelpoel[6] suggest that the split sound results from dilatation of the pulmonary artery. Others have noted a split or accentuated first sound at the base of the heart (Lian and Welti,[7] who quote Petit[8]; Dow and associates,[9] and Greene and associates[10]). In contrast Abrahams and Wood[3] stated that there was nothing remarkable about the first heart sound in any of their 37 cases; and Mannheimer and Jonsson[11] said that the amplitude of the first heart sound, even in the most severe cases, was not pathologic. If our explanation of the split or accentuated first sound is correct, we believe it will occur more commonly in mild cases with some mobility of the cone-shaped, stenotic pulmonary valve.

References to pulmonary stenosis with a normal aortic root in senescent patients are infrequent,[12-14] and we have found only one reference to cardiac catheterization data[15] obtained from a 58-year-old woman who died two years later as a result of her congenital pulmonic valvular stenosis.[16] She was seriously ill with recurrent ascites and atrial fibrillation, and so her clinical picture bears no resemblance to those of our three patients. The right ventricular and pulmonary artery pressures were 184 to 207/11 to 23 and 12 to 18/6 to 11 mm. Hg, respectively (cf. Table I). Our own findings at cardiac catheterization would have more value if we could know what these pressure levels had been twenty years previously. Our inference that they have not changed significantly is supported by the histories, which give no evidence of gradual deterioration that could be accounted for by pulmonic valve stenosis. Furthermore, roentgenograms of M.C. (Fig. 4) show no significant change over a fifteen-year period, and the standard leads of her electrocardiogram are identical with those taken eleven years before. After observing these three patients, we have made the diagnosis in two other middle-aged patients who were unwilling to undergo cardiac catheterization.

The hemodynamic data from these three patients differ from those in patients with severe pulmonary valve stenosis. Mean pulmonary artery pressure and pulse pressure were not reduced. This suggests that the right ventricle had hypertrophied enough to compensate for the stenosis and to maintain a normal or nearly normal minute volume cardiac output at rest (Table I). The response to exercise was not studied because two patients had had chest pain quite recently and the third could not be persuaded to exercise.

In only one of our three patients were the fluoroscopic and radiographic interpretations correct prior to definitive diagnosis by cardiac catheterization. Patent ductus arteriosus and idiopathic dilatation of the pulmonary artery were the two inaccurate roentgenographic interpretations. Another condition that must be considered in the differential diagnosis for this age group is cor pulmonale. The findings described in these three patients at fluoroscopy and on radiographic examination were accurate, but the interpretation of the findings was not, probably because congenital heart disease in this age group is uncommon. Naturally, a higher percentage of correct diagnoses will be made if one is alert to this possibility. Degenerative changes in the heart, great vessels, and smaller pulmonary vessels add to the difficulties in making an accurate diagnosis. However, when due consideration is given to the history, physical examination, electrocardiogram, and roentgenologic observations, the diagnosis can be made clinically. The definitive supporting evidence is furnished by cardiac catheterization and hemodynamic recording.

CONCLUSION

No broad generalizations are permissible from the clinical and physiologic observations on our three elderly patients with pulmonic stenosis. We suggest that if a patient with this congenital defect has (1) a nearly normal minute volume cardiac output at rest, (2) a right ventricular systolic pressure of 100 mg. Hg or less, (3) a normal pulmonary artery pressure, and (4) no symptoms referable to his heart anomaly, he probably will be able to lead a reasonably active life until after middle age.

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EFFECT OF MILD, STEADY STATE EXERCISE ON TOTAL PULMONARY RESISTANCE OF NORMAL SUBJECTS AND THOSE WITH ISOLATED AORTIC VALVULAR LESIONS

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THERE has been recent evidence to show that the pulmonary arterial pressure rises or decreases slightly as the result of mild exercise in patients with normal hearts[7,11,12] and consistently rises in those in congestive failure.[1,3,6,7,9] However, there has been much variation in the body of reported data, particularly in regard to the calculation of resistances, which imposes difficulties upon interpretation of the results. This may have been due in part to the lack of recognition of the importance of steady state for the validity of cardiac output determination by the Fick principle,[4] to the lack of clear definition and standardization of the exercise procedure and the imposed work load, and to the unitarian handling of groups of patients with solitary or combined heart lesions in various stages of compensation.

The purpose of this study was to investigate the effect of mild, steady state exercise on the general and cerebral hemodynamics of normal patients and those with "*pure,*" *isolated aortic insufficiency or stenosis.* The present report will deal only with those findings pertaining to general hemodynamics; the details of cerebral hemodynamics, other than for the necessary allusion to methodology, will be presented in subsequent communications.[10] An effort has been made to standardize external work for the sake of uniform comparison, while recognizing the inability to control differences in internal energy expenditure.

MATERIAL AND METHODS

Of 36 studies performed, 27 were selected for analysis and presentation. Five studies were discarded because of failure to achieve a reasonable measure of steady state either during the control or the exercise periods, 2 because of poor checks of duplicate blood oxygen determinations, and 2 in which pressure tracings were technically too poor to measure. Four of the control studies and 5 of the studies on cardiac patients were discarded.

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Nine of the 27 patients were control subjects who had convalesced from various medical illnesses and, with the exception of one (H.B.) who had moderately severe pulmonary emphysema, were free of cardiorespiratory disease, were afebrile and nonanemic. Nine of the 18 cardiac patients had aortic stenosis and 9 had aortic insufficiency, as determined by repetitive physical examination and the usual accepted clinical criteria. Some of the cardiac patients had not exhibited evidence of congestive failure at the time of investigation; the remainder, previously in failure, were studied only upon being considered clinically compensated at rest following a regime of medical therapy. All of these subjects had cardiac (predominantly left ventricular) enlargement as demonstrated roentgenographically. Because this was an age group older than the control patients, many had mild grades of emphysema. All patient material was studied as it became available from the wards of Cleveland City and Crile Veterans Administration hospitals.*

By serial oxygen consumptions performed the day prior to the study, a determination was made in each patient of the amount of leg exercise in the supine position required to achieve a steady state within 8 to 10 minutes, and to maintain it for an additional 20 minutes. The work load varied between 715 and 877 foot-pounds per minute, and averaged 807 and 759 foot-pounds per minute in the control and the cardiac subjects, respectively. The apparatus employed was a variable resistance bicycle ergometer with a stroke radius of 18 cm.† and with knee flexion not exceeding 80 degrees from the horizontal. All exercise was done at 40 r. p. m. timed with a metronome, and the work load found to meet the steady state requirements outlined above was maintained uniform in each patient study.

Following evening (phenobarbital, 0.032 Gm.) and morning (pentobarbital sodium, 0.1 Gm.) sedation, the patients were catheterized in routine fashion in the postabsorptive state at an ambient temperature of 23° to 24° C. employing No. 7 Fr. Cournand catheters which were made to rest just within the right pulmonary artery. A No. 19 intra-arterial needle was introduced into the brachial artery for the collection of peripheral arterial blood samples. Following stabilization, several determinations were made of pulmonary and brachial artery pressure and heart rates. The wedge pressure was recorded at rest in all subjects, and during exercise in only 4 patients. Wedge pressures are considered normal when less than 10 mm. Hg, and abnormally elevated when above 12 mm. Hg. Individual exceptions occur, but the criteria are considered valid when applied to groups of patients.

An indwelling needle was then introduced into the jugular bulb for the later determination of cerebral blood flows. Sufficient time was permitted to elapse to restore pressures and heart rates to prejugular puncture levels. When these had stabilized over the course of 20 to 30 minutes, the pre-exercise studies, consisting of 2 matched pressure recordings and 2 cardiac outputs, were performed. Following jugular puncture the original basal state was not fully re-

*Crile Hospital patients were made available through the courtesy of Drs. H. Schwartz and N. Shumway.

†Gilmore Industries, Inc., 5713 Euclid Ave., Cleveland, Ohio.

stored in 3 of the control and 1 of the cardiac patients, as evidenced by slight but constant elevations in central and peripheral pressures and heart rates. However, given the matched oxygen consumptions and cardiac outputs which varied less than 10 per cent,[4] these were accepted as representing at least valid control steady state determinations. All reported values for the cardiac indices represent the average of 2 consecutive determinations which differed less than 10 per cent from each other.

Cerebral blood flow determination was then performed and the patients were then exercised. Cardiac output and pressure readings were repeated during the 10-to-12- and 12-to-14-minute periods and were immediately followed by a second determination of cerebral blood flow. A final oxygen consumption was done to verify maintenance of the steady exercise state at the termination of the study.

Pressures were transduced via Statham strain gauges and inscribed on the Brush multichannel oscillograph. The reference point for central venous and wedge pressures was 10 cm. above the posterior surface of the thorax in the fourth intercostal space. Expired air was measured through a dry gas test meter, 2-minute collections made in Douglas bags, oxygen analysis obtained through the Pauling Oxygen Analyzer, and ultimate values corrected for STP to 0° C. and 760 mm. Hg. Because of the negligible correction factor,[1] and the mild degree of exertion, expired air during exercise was accepted as measured.

Blood specimens for oxygen analysis were obtained in duplicate with each oxygen consumption, and oxygen contents determined spectrophotometrically by the method of Hickam and Frayser.[8] Duplicate determinations were required to match within 0.2 vol. per cent.

All pressures represent the average of 2 or 3 recordings obtained immediately prior to and following the respective oxygen consumptions. Mean pressures were obtained by planimetric integration. Total pulmonary (Pu.T.R.) and peripheral (E.T.P.R.) resistances, disregarding the calculation of pressure gradients in the former, were derived according to standard formulas[5] and expressed as c.g.s. units/$^{-5}$. The upper limit of normal for Pu.T.R. in this laboratory is 260 c.g.s. units.

RESULTS

For the purpose of presentation, analysis, and discussion, the data are divided into 3 groups: the control subjects (9 patients, Group 1, Table I), the subjects with heart disease whose resting wedge pressures were less than 10 (5 patients, Group 2, Table II), and those whose wedge pressures were greater than 12 mm. Hg (11 patients, Group 3, Table III). Two of the cardiac patients had borderline wedge pressures, and their data are appended to those of Group 2, though not included in averages and analyses. Averages and significance analyses (Fisher's 't' test, groups less than 30), are presented in Table IV.

1. *Heart and Respiratory Rates.*—These did not vary significantly in the three groups, and showed almost identical increases on exercise.

2. *Oxygen Consumption.*—The average resting values were virtually identical in the three groups. Exercise produced a highly significant increase in oxygen uptake in all groups, but no significant difference when compared to each other.

TABLE I. HEMODYNAMIC DATA IN NORMAL CONTROL PATIENTS (GROUP 1)

TABLE I. HEMODYNAMIC DATA IN NORMAL CONTROL PATIENTS (GROUP 1)

Pt. Data		Diagnosis		H. R.	R. R.	$O^2C/M.^2$	AVD	C. I.	P_{RA}	P_{RV}	P_{PA}	P_{BA}	PC	Pu. T. R.	ETPR
D. H.	N M	Br. Pn. RLL	R	87	16	121	3.48	3.48	4/1(3.1)	23/3(9.4)	28/9(14.9)	120/84(90.5)	10.3	193	1164
44	799		E	87	22	241	5.43	4.45	– –	– –	28/5(14.7)	144/90(107.0)	–	149	1086
1.77	$M.^2$		%			+99.2	+56.0	+26.7						–22.8	–6.7
D. H.	W M	Br. Pn. RUL	R	88	16	122	3.95	3.04	5/3(3.9)	22/5(11.7)	20/11(14.8)	108/67(82.5)	5.7	224	1253
40	799		E	94	18	201	5.59	3.59	– –	– –	18/10(14.5)	109/67(84.2)	–	184	1071
1.75	$M.^2$		%			+64.7	+41.5	+18.1						–17.8	–14.4
W. B.	W M	Alcoholic	R	72	12	123	3.37	3.67	7/5(5.5)	25/5(11.9)	28/14(21.4)	120/76(96.6)	4.6	254	1145
48	799		E	80	16	239	5.08	4.72	– –	– –	29/17(23.2)	117/75(95.5)	–	213	879
1.84	$M.^2$		%			+94.2	+50.7	+28.6						–16.1	–23.1
H. B.	W M	Peptic ulcer	R	84	12	88	3.77	2.35	7/4(5.6)	30/6(13.6)	32/13(22.5)	138/81(100.0)	9.9	456	2087
42	799		E	88	20	225	5.56	4.06	– –	– –	38/12(25.0)	129/75(101.0)	–	290	1183
						+155.7	+47.5	+72.8						–36.4	–41.1
A. P.	W M	Br. Pn. RUL	R	82	16	144	3.58	4.02	5/3(3.7)	19/3(10.3)	26/12(16.9)	121/76(86.5)	7.2	176	900
54	715		E	84	24	295	6.35	4.66	– –	– –	29/11(17.9)	138/83(101.2)	–	161	910
1.91	$M.^2$					+104.9	+77.4	+15.9						–8.5	+1.1
C. D.	N M	CNS syphilis	R	72	20	126	4.63	2.73	5/3(3.9)	27/6(11.7)	29/12(18.6)	132/78(93.0)	6.4	258	1292
42	877		E	90	24	232	6.00	3.84	– –	– –	25/6(15.2)	130/81(99.0)	–	150	977
2.11	$M.^2$		%			+84.1	+29.6	+40.7						–41.8	–24.3
J. F.	N M	Br. Pn. RUL	R	88	16	129	3.52	3.66	6/3(4.8)	23/3(9.8)	23/10(14.5)	119/74(90.0)	4.6	170	1056
42	799		E	90	17	218	5.24	4.16	– –	– –	22/10(14.6)	126/83(97.1)	–	150	1003
1.86	$M.^2$		%			+69.0	+48.9	+13.7						–11.8	–5.0
F. A.	W M	Anxiety	R	67	16	127	4.39	2.90	6/3(4.9)	25/5(10.3)	17/8(12.7)	111/73(85.7)	8.3	200	1352
28	877	neurosis	E	77	22	185	5.02	3.69	– –	– –	20/9(14.7)	115/75(91.4)	–	182	1132
1.75	$M.^2$		%			+45.7	+14.3	+27.2						–9.0	–16.2
H. L.	W M	Alcoholic	R	88	18	132	4.68	2.80	5/1(1.7)	18/0(7.4)	21/12(14.1)	146/95(108.1)	7.0	251	1927
57	799		E	92	20	197	5.48	3.60	– –	– –	24/12(16.5)	144/94(110.7)	–	229	1539
1.60	$M.^2$		%			+49.2	+17.1	+28.6						–8.8	–20.1

Average age, 44 years; average work load, 807 foot-pounds per minute.

Key: Patient Data: Initials, race and sex, age, work load, square meters of body surface. H. R., heart rate; R. R., respiratory rate; $O^2C/M.^2$, oxygen consumption, c.c./$M.^2$/min.; AVD, arteriovenous oxygen difference in v.p.c.; C.I., cardiac index; $P_{RA, RV, PA, BA, PC}$, pressure in right atrium, ventricle, pulmonary artery, brachial artery, wedge pressure; Pu.T.R., pulmonary total resistance; ETPR, total peripheral resistance. R, at rest; E, during exercise; percentile changes underscored. Mean pressures in parentheses.

TABLE II. HEMODYNAMIC DATA IN CARDIAC PATIENTS WHO WERE NOT IN FAILURE (GROUP 2)

Pt.	Data	Diagnosis		H. R.	R. R.	O²C/M.²	AVD	C. I.	P_{RA}	P_{RV}	P_{PA}	P_{BA}	PC	Pu. T. R.	ETPR
G. J.	N M	A. I. NPF,	R	73	18	114	5.00	2.29	3.5/1(1.7)	24/4(9.1)	25/6(13.1)	108/54(77.5)	6.4	265	1572
57	760	No Dig.	E	82	20	183	6.00	3.03	4/3(3.9)	– –	32/10(15.5)	132/72(97.5)	–	238	1494
1.72	M.²		%			+60.5	+20.0	+32.3						–10.1	–5.0
L. B.	N M	A. I. NPF,	R	72	16	129	4.54	2.84	4/3(3.9)	22/3(8.9)	22/9(14.7)	137/68(91.2)	6.6	267	1656
23	799	On Dig.	E	77	18	170	5.11	3.32	– –	– –	22/10(15.3)	141/59(92.7)	6.4	237	1439
1.55	M.²		%			+31.2	+12.5	+16.9						–11.2	–13.1
E. K.	N M	A. I. NPF,	R	64	14	117	5.27	2.23	5/3(3.8)	23/3(9.1)	32/11(18.1)	173/75(101.0)	6.1	324	1810
55	741	On Dig.	E	64	18	187	7.15	2.62	– –	– –	34/12(19.2)	168/70(86.3)	–	292	1315
2.00	M.²		%			+59.8	+35.7	+17.4						–9.8	–27.8
J. B.	W M	A. S. NPF,	R	67	12	116	5.83	1.98	5/2(2.6)	29/4(11.2)	29/11(17.3)	87/48(64.2)	8.4	333	1236
54	780	On Dig.	E	76	18	192	6.78	2.83	– –	– –	37/13(20.4)	111/63(79.7)	–	274	1071
2.10	M.²		%			+65.5	+16.3	+42.9						–17.7	–13.3
P. J.	W M	A. S. PF	R	71	15	134	3.26	4.04	6/3(4.6)	26/4(10.6)	27/10(15.7)	135/57(85.0)	7.1	161	871
64	760	On Dig.	E	83	19	232	4.42	5.25	– –	– –	33/11(18.2)	150/60(90.0)	–	144	713
1.93	M.²		%			+73.1	+35.6	+29.0						–10.5	–10.5

Average age, 51 years; average work load, 768 foot-pounds per minute.

Hemodynamic Data in Patients With Borderline Wedge Pressures; Data Not Included in Averages and Analyses

L. H.	N M	A. I. NPF	R	100	16	130	6.34	2.05	5/2(2.8)	32/5(14.1)	32/14(19.6)	198/117(135.3)	11.3	442	3054
54	838	No Dig.	E	100	20	252	9.44	2.67	– –	– –	41/18(25.8)	214/116(148.9)	–	446	2751
1.73	M.²		%			+93.8	+48.9	+23.2						+0.9	–9.9
T. P.	W M	A. S. PF	R	78	20	107	6.78	1.58	4/1(1.7)	20/3(7.4)	24/10(14.3)	103/63(77.2)	11.6	407	2211
67	715	On Dig.	E	92	40	244	10.96	2.23	– (1.0)	– –	36/13(20.4)	123/64(84.0)	–	414	1705
1.77	M.²		%			+128	+61.6	+41.1						+1.7	–22.9

Key: A.I., aortic insufficiency; A.S., aortic stenosis; NPF, no previous failure; PF, previous failure; No Dig., no digitalis; On Dig., on digitalis. (Otherwise, as in Table II.)

TABLE III. HEMODYNAMIC DATA IN CARDIAC PATIENTS WHO WERE IN FAILURE (GROUP 3)

Pt.	Data	Diagnosis		H. R.	R. R.	O²C/M.²	AVD	C. I.	P_{RA}	P_{RV}	P_{PA}	P_{BA}	PC	Pu. T. R.	ETPR

TABLE III. HEMODYNAMIC DATA IN CARDIAC PATIENTS WHO WERE IN FAILURE (GROUP 3)

Pt.	Data	Diagnosis		H. R.	R. R.	$O^2C/M.^2$	AVD	C. I.	P_{RA}	P_{RV}	P_{PA}	P_{BA}	PC	Pu. T. R.	ETPR
A. N.	N M	A. I., PF	R	78	18	124	3.80	3.26	5/2(3.3)	45/3(16.1)	45/23(31.3)	232/105(158.5)	14.1	457	2367
50	741	On Dig.	E	82	20	176	5.44	3.24	– –	– –	48/21(32.4)	247/100(153.0)	–	487	2303
1.64	$M.^2$		%			+41.9	+43.2	−0.6						+6.5	−2.8
J. S.	W M	A. I., PF	R	88	20	157	4.78	3.29	6/2(4.5)	29/5(11.9)	29/11(18.4)	162/63(99.1)	13.2	271	1460
70	799	No Dig.	E	108	24	287	6.92	4.20	– –	– –	43/20(28.9)	183/63(118.8)	–	333	1370
1.65	$M.^2$		%			+82.8	+44.8	+27.6						+22.8	−6.2
J. C.	W M	A. I., PF	R	83	20	127	4.89	2.60	12/7(10.4)	—— ——	46/17(35.6)	162/48(101.9)	18.8	660	1932
53	741	On Dig.	E	90	24	209	6.06	3.33	– –	– –	67/30(50.5)	210/69(145.1)	24.2	720	2069
1.62	$M.^2$		%			+64.6	+23.9	+33.0						+9.0	+7.1
H. P.	N M	A. I., PF	R	108	20	118	6.61	1.78	9/6(6.4)	68/8(28.2)	67/28(45.0)	132/40(74.4)	19.1	1081	1788
60	741	On Dig.	E	106	22	171	8.63	1.98	– –	– –	88/47(59.2)	138/48(85.4)	–	1275	1840
1.87	$M.^2$		%			+44.9	+30.6	+11.0						+17.9	+2.9
M. H.	W F	A. I., PF	R	89	20	120	3.00	4.02	AF (6.1)	30/7(17.5)	29/12(20.2)	150/48(88.8)	13.4	268	1178
57	760	On Dig.	E	96	24	181	4.29	4.20	– –	– –	38/18(27.9)	162/52(99.1)	18.0	354	1257
1.50	$M.^2$		%			+50.8	+43.0	+4.4						+32.0	+6.7
P. G.	W M	A. S., PF	R	84	16	103	6.28	1.65	6/2(4.4)	20/3(13.5)	32/11(18.3)	102/48(68.5)	13.7	569	2132
78	780	On Dig.	E	94	20	174	7.53	2.31	– (5.8)	44/3(20.2)	44/21(28.8)	90/42(63.0)	–	638	1396
1.56	$M.^2$		%			+68.9	+19.9	+40.0						+12.1	−34.5
M. M.	W F	A. S., NPF	R	84	20	96	4.10	2.34	10/4(6.0)	28/4(11.3)	33/14(22.4)	105/42(67.5)	16.2	484	1459
40	741	On Dig.	E	94	24	161	6.10	2.63	– –	– –	34/19(28.2)	120/48(75.0)	–	541	1439
1.58	$M.^2$		%			+67.7	+48.8	+12.4						+11.8	−1.4
L. N.	W M	A. S., PF	R	83	18	102	5.69	1.79	6/3(4.4)	44/5(19.1)	43/24(30.2)	114/66(78.6)	16.9	846	2204
62	760	On Dig.	E	92	20	214	8.53	2.51	– –	– –	50/37(44.2)	118/72(82.5)	–	885	1652
1.59	$M.^2$		%			+109.8	+49.9	+40.2						+4.6	−25.1
H. B.	W M	A. S., PF	R	93	16	115	6.23	1.85	12/10(11.2)	56/11(25.1)	55/22(35.5)	136/88(106.0)	14.1	902	2477
64	741	On Dig.	E	100	20	167	9.06	1.84	15/12(13.1)	69/15(32.7)	70/32(46.4)	142/91(107.3)	18.1	1184	2738
1.70	$M.^2$		%			+45.2	+45.4	00.0						+31.3	+10.5
C. C.	W M	A. S., PF	R	82	16	127	5.81	2.18	9/6(6.5)	32/8(16.0)	37/23(31.3)	133/55(70.0)	19.4	712	1594
61	715	On Dig.	E	88	24	212	7.36	2.88	– –	– –	60/40(51.4)	139/56(87.6)	–	886	1509
1.61	$M.^2$		%			+66.9	+26.7	+32.1						+24.4	−5.6
P. K.	W M	A. S., PF	R	67	15	107	4.59	2.35	6/3(4.8)	31/5(14.9)	31/15(21.5)	187/115(130.0)	14.2	423	2557
63	760	On Dig.	E	80	19	230	8.57	2.69	– –	– –	40/25(33.2)	213/138(163.0)	–	571	2801
1.73	$M.^2$		%			+114.9	+86.7	+14.5						+35.0	+9.5

Average age, 60 years; average work load, 753 foot-pounds per minute.
Key: As in Tables I and II.

TABLE IV. AVERAGES AT REST, DURING EXERCISE, PERCENTILE CHANGES, AND SIGNIFICANCE DETERMINATIONS

	H. R. /min.	R. R. /min.	$O^2C/M.^2$ (c.c./min.)	AVD (v.p.c.)	C. I. (L./min.)	Pu. T. R. (c.g.s.)	ETPR (c.g.s.)
Group 1							
R	81	16	124	3.93	3.18	242	1346
E	87	20	225	5.53	4.09	190	1087
%	+7.4	+25.0	+82.2	+40.7	+28.6	−21.5	−19.2
p	—	—	<.001	<.001	<.001	<.02>.01	<.02>.01
Group 2							
R	69	15	122	4.78	2.68	270	1429
E	76	20	193	5.89	3.41	237	1206
%	+10.0	+24.0	+58.2	+23.2	+27.2	−14.0	−18.4
p	—	—	<.001	<.001	<.001	<.001	<.001
Group 3							
R	78	18	118	5.07	2.46	607	1922
E	85	22	198	7.13	2.89	716	1852
%	+9.0	+22.2	+67.8	+40.6	+17.4	+17.9	−3.7
p	—	—	<.001	<.001	<.001	<.001	<0.8
Significance Comparison of Group 1 vs. Group 2 and Group 1 vs. Group 3							
1-2 p	—	—	<.1>.05	<.1>.05	<.7>.6	<.5>.6	<.7>.6
1-3 p	—	—	<.7>.6	<.2>.1	<.001	<.001	<.2>.1

3. *Arteriovenous Oxygen Difference.*—There were highly significant increases in all three groups as compared to their control values, but again there was no significant difference when compared to each other. However, the average resting A-V difference was least in the control (3.93 v.p.c.), greater in Group 2 (4.78 v.p.c.), and highest in Group 3 (5.07 v.p.c.) patients.

4. *Cardiac Index.*—This was highest in the control group, lower in Group 2, and lowest in Group 3. Exercise produced a highly significant increase in all groups. The increase was similar in Groups 1 and 2 (+28.6 and +27.2 per cent, respectively), but considerably less in Group 3 (+17.4 per cent). This lesser increase was statistically highly significant when compared to the normal subjects and the Group 2 patients.

5. *Pulmonary Artery Pressure.*—This increased in most of the normal subjects, and in all of the patients in Groups 2 and 3. Three subjects in Group 1 showed slight decreases. It is noteworthy that the least increases occurred in Groups 1 and 2, and the most marked increases in Group 3.

6. *Wedge Pressure.*—The resting mean wedge pressure was less than 10 mm. Hg in the control subjects and (arbitrarily) in the Group 2 patients; it was greater than 12 mm. Hg (arbitrarily) in the Group 3 patients. It was measured only four times during exercise, in one Group 2 and in three Group 3 patients. In the former instance it remained virtually unchanged (6.6 to 6.4 mm. Hg), and in the latter cases it increased (18.8 to 24.2, 13.4 to 18.0, and 14.1 to 18.1 mm. Hg).

7. *Total Pulmonary Resistance.* (*Pu.T.R.*).—This was initially normal in Group 1 (242 c.g.s.), slightly elevated in Group 2 (270 c.g.s.), and markedly elevated in Group 3 (607 c.g.s.). Pu.T.R. decreased constantly and significantly in both Groups 1 and 2, although a greater but not significantly different decrease was registered in the Group 1 subjects (−21.5 and −14.0 per cent, respectively) as compared to those in Group 2. It increased in each instance and significantly in all patients in Group 3 (+17.9 per cent), and the observed increase was significantly different from the decreases registered in the other groups. This epitomizes the similarity in response among both control and Group 2 patients on the one hand and those cardiac subjects with elevated wedge pressure on the other.

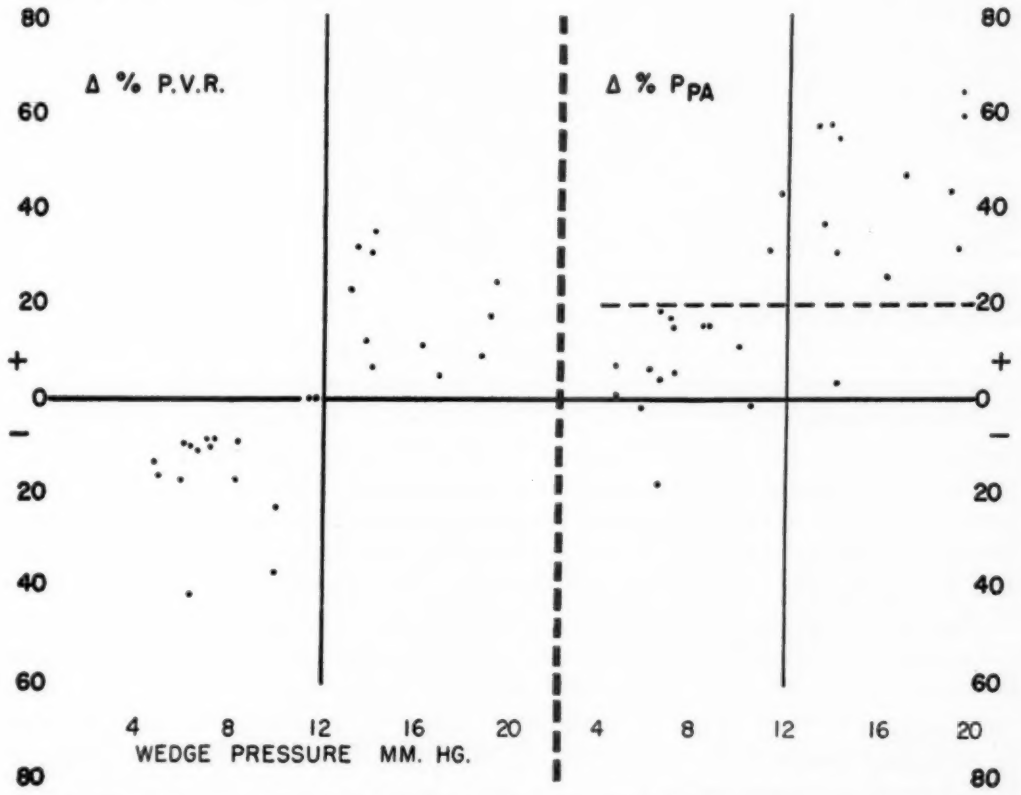

Fig. 1.—Relationship between the resting wedge pressures and the percentile changes in pulmonary artery pressure and Pu.T.R. The two subjects who showed virtually no change in Pu.T.R. and whose wedge pressures were borderline are noted. One subject with elevated wedge pressure likewise falls within the normal pulmonary artery pressure range. There is no direct correlation between the actual level of the wedge pressure and the changes in the two parameters (r = < 0.3200).

The two patients who had borderline wedge pressures (L.H. and T.P., Table II), showed no change in resistance on exercise (442 to 446 c.g.s., and 407 to 414 c.g.s., respectively).

Fig. 1 illustrates the relationship between the wedge pressures and the percentile changes in Pu.T.R. and pulmonary arterial pressure. There was, however, no direct correlation between the height of the wedge pressure and the percentile changes in either parameter (r = < 0.3200).

8. *Brachial Artery Pressure and Total Peripheral Resistance.*—These did not vary in the observed changes from the results obtained by others. It may be noted, however, that the observed changes bore no particular relationship to the changes in pulmonary artery pressure and Pu.T.R. in these experiments.

DISCUSSION

The results of these experiments confirm the original observations of Riley and associates[11] that mild, steady state exercise is attended by a decrease in Pu.T.R. in normal subjects. These investigators likewise showed that normal man may thus tolerate a threefold increase of the basal venous return without undue rise in pulmonary artery pressure and with a decrease in Pu.T.R. Edwards[2] has demonstrated that in the open chest dog preparation pulmonary resistance varies inversely to the volume blood flow. It is not surprising, therefore, that this should obtain in normal man as long as (a) volume blood flow is not so great as to increase excessively the volume elasticity coefficient ratio of the vascular bed, necessitating an abnormal increase of right ventricular to left atrial pressure gradient, and (b) there is functional integrity of the left side of the heart. In the normal subjects the former requirement was met by the selection of a mild degree of exercise, which likewise insured the prolonged maintenance of a steady exercise state, and the latter was provided by the functional status of the patients themselves.

The subjects with valvular aortic lesions whose resting wedge pressures were less than 10 mm. Hg were inferentially considered to have normal left ventricular end-diastolic pressures. Their response to exercise was similar to that of the control group in all parameters that were measured, with only slight rises in pulmonary artery pressure and a decrease in Pu.T.R. This would indicate that sufficient left ventricular reserve existed to meet a mild exercise load in normal fashion, although it is possible that some may not have responded in a similar manner on more severe exercise. The finding of a response similar to that of the normal subjects, however, corroborates the clinical histories in these patients. Four of the five in Group 2 had had no complaints referable to the cardiovascular apparatus on everyday exertion, though all had "roentgenographically" enlarged left ventricles. Three had been given digitalis only because their hearts were enlarged. Another (P.J., Table II) had been asymptomatic until one week prior to admission, when the combination of bronchopneumonia and a suddenly great dietary salt intake brought on severe breathlessness on exertion without edema.

By contrast, the 11 patients in Group 3, all of whom had elevated wedge pressures at rest, responded with excessive increases in pulmonary artery pressure and a rise in Pu.T.R. even with the very mild amount of exercise employed. Measurements of the wedge pressure during exercise were carried out in only 3 patients, but it increased in all instances. It may be reasonably assumed that these subjects with solitary aortic valvular lesions had increased or borderline elevations of the left ventricular end-diastolic pressure with associated increases in left atrial and mean pulmonary arterial pressures and Pu.T.R. at rest. In their case the left ventricle, already decompensated at rest, was not

able to meet the added demand imposed by exercise, with the resultant development of further decompensation. Since at least five of these subjects had normal right ventricular end-diastolic pressures at rest, one can only conclude that exercise produced a backward failure of the left ventricle.

It would also appear from the data that resting measurements of the pulmonary artery pressure, the cardiac index, and the Pu.T.R. alone are not always adequate in assessing the functional status of these subjects. This may in part be due to the 10 per cent error one must accept in Fick determinations, with an even greater error reflected in calculated resistances. Pulmonary artery pressure alone may be difficult to assess since it is partly dependent on the volume of venous return and on intrathoracic pressure changes, in addition to being responsive to back-pressure phenomena. Pulmonary artery pressure was slightly elevated in several Groups 1 and 2 patients, and only slightly elevated in three of the Group 3 patients (J.S. and M.H.). In addition, Pu.T.R. calculations at rest may be difficult to interpret individually. In several instances it was well above the "upper limit of normal" in several Group 2 and only slightly elevated in two Group 3 subjects (J.S., M.H., and P.G.). Pu.T.R. determinations obtained during exercise, however, clearly separate the Group 3 subjects as a cardiodynamic family distinct from the control and the "compensated" patients. These relations are summarized in Table V.

TABLE V. MEAN AND STANDARD ERROR IN THE INDIVIDUAL DATA, RESTING AND EXERCISE, FOR THE CARDIAC INDEX AND PU. T. R.

	REST			EXERCISE		
	GROUP 1	GROUP 2	GROUP 3	GROUP 1	GROUP 2	GROUP 3
Cardiac index	3.18 ±0.18	2.68 ±0.37	2.46* ±0.23	4.08 ±0.14	3.41 ±0.47	2.89* ±0.24
Pu. T.R.	242 ±29.0	270 ±30.0	607† ±78.8	190 ±15.8	237 ±28.0	716† ±94.0

*Signifies significant difference from Group 1 only.
†Signifies significant difference from both Groups 1 and 2.

All of the patients in Group 3 except one (M.M.) had been in clinically recognizable congestive failure, had been digitalized (except J.S.), and clinically were thought to be fully compensated at rest by the time the experiments were conducted. Moreover, they did not appear to be grossly abnormal or uncomfortable during routine ward activities. This was borne out by the observed ventilation during the experiments (not included in Tables I-III). Group 1 patients had a mean ventilation of 3.59 L./M.^{2}/min., and on exercise this increased to 6.07 L./M.^{2}/min., an increment of 69.1 per cent. Comparable figures in the Group 3 patients were 3.84 and 6.00 L./M.^{2}/min., an increment of 56.2 per cent. This lower increment may be explained by the slightly lesser amount of exercise employed in the latter subjects (807 and 759 foot-pounds per minute,

respectively). Grossly, this slight difference in ventilation, both at rest and during exercise, could not be detected during the experiments.

From these observations, two additional clinical corollaries emerge: (1) It may not be possible to detect mild left ventricular failure in such patients by clinical observation at rest and during reduced ward activity. (2) The data corroborate the time-honored clinical observation that once a patient with an aortic valvular lesion has decompensated, as the sole result of the lesion, rarely can he return to the level of activity which was possible before his breakdown. This is at variance with the natural history of mitral stenosis where many factors other than ventricular decompensation may play a role in the genesis of temporary failure.

SUMMARY AND CONCLUSIONS

Mild steady state exercise produced a consistent decrease in the total pulmonary resistance (Pu.T.R.) and little or no increase in the pulmonary artery pressure in all of nine normal subjects who were studied. Similar findings were noted in these experiments in five subjects with isolated aortic valvular lesions in whom the resting wedge pressures were less than 10 mm. Hg. In the eleven subjects with isolated aortic valvular lesions in whom the resting wedge pressures were greater than 12 mm. Hg, exercise produced excessive increases in pulmonary artery pressure in all but one, and consistent increases in Pu.T.R. Two subjects with wedge pressures between 10 and 12 mm. Hg showed marked rises in pulmonary artery pressure but virtually no change in Pu.T.R.

Evidence is adduced which demonstrates that following apparent compensation from gross congestive failure, subjects with aortic valvular lesions may often maintain a mild degree of cardiodynamic failure which may not be readily appreciated by the usual clinical observations at rest and during the course of mild hospital ward activity.

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AN ACCURATE LEAD SYSTEM FOR SPATIAL VECTORCARDIOGRAPHY

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DATA have been previously presented[1,2] which indicate that it is feasible to obtain leads which possess relatively uniform vector properties for all points within the myocardium where electromotive forces are generated. The equation for defining the voltage (V) of such a theoretically perfect vectorcardiographic lead is:

$$V = 1_x (e_{1x} + e_{2x} + \ldots + e_{nx}) + 1_y (e_{1y} + e_{2y} + \ldots + e_{ny}) + 1_z (e_{1z} + e_{2z} + \ldots + e_{nz}) \quad (1)$$

where the 1 terms represent the orthogonal components of the identical lead vectors and the e terms represent the orthogonal components of each of the individual dipoles located at n separate locations. Since the e terms are scalar rather than vector quantities, they may be summated arithmetically, e.g., $e_x = e_{1x} + e_{2x} + \ldots + e_{nx}$. It is, therefore, possible to disregard the separation of the individual dipoles of the cluster and to write the equation

$$V = 1_x e_x + 1_y e_y + 1_z e_z \quad (2)$$

which is identical in form to that which is applicable when it is postulated that a dipole cluster may be represented by a single equivalent dipole.[3] It should be emphasized, however, that Equation 2 has been derived without making the assumption of a single equivalent dipole in the manner in which this concept is usually applied. In the derivation of Equation 2 the dipole cluster is in effect replaced mathematically by an equivalent dipole which exists only for the lead in question. There is no requirement that the equivalent dipole can or should be substituted for the cluster when any one of an infinite number of other possible leads is utilized. Thus Equation 2 is possible because of the manner in which the lead ($\vec{1}$) is constructed.

Let it be assumed that a lead of the type defined by Equation 2 could be developed in which 1_y and 1_z were each zero. The voltage (V_x) recorded by such a lead is then obtained by the expression:

$$V_x = 1_x e_x \quad (3a)$$

Similarly, if two other leads could be devised having vectors parallel to the y and

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z coordinate axes, respectively, equations identical in form to that of Equation (3a) could be written as follows:

$$V_y = 1_y e_y \tag{3b}$$

$$V_z = 1_z e_z \tag{3c}$$

The purpose of the present communication is to describe leads which possess properties approximating those defined by Equations 3a, 3b, and 3c. To recapitulate, these properties are two: (1) uniformity of lead vectors for all points in the myocardium, and (2) parallel directions of orthogonal coordinate axis and respective lead axis. A third characteristic which is desirable, but not essential, is equality of the magnitudes of 1_x, 1_y, and 1_z.

It has been previously demonstrated[1,2] that certain leads recorded between networks of points possess greater lead-vector uniformity for all dipoles of a cluster than other leads with similar anatomic orientation recorded between single points. In the case of leads with electrodes distributed in practical network systems along an arc over the precordium where the latter is intersected by a transverse plane through the torso, the coefficient of variation of the vectors of such a lead is substantially smaller than those coefficients of certain leads forming the cube or the tetrahedron.[2] It is reasonable to assume that similar networks of points extending two dimensionally over the body surface could be used to form leads, the vector uniformity of which would be at least as satisfactory as that calculated for leads formed by electrode networks distributed along arcs.

In the development of suitable vectorcardiographic leads the data published by Frank[4,5] have been freely utilized. The two main sources of these data are Table I of Reference 4 and Figs. 2,*A*, *B*, and *C* of Reference 5 (supplemented by Fig. 2 of Reference 4). From the first source it has been demonstrated[2] that a lead between point M at level 6 of Frank's model and a network of points C, D, E, F, and G at the same level, joined through equal resistors, has a coefficient of variation of 16.8 per cent when applied to the 71 dipole locations on the transverse plane of level 6. It was likewise demonstrated[2] that a lead between point I and a network of points O, P, A, B, and C possesses a coefficient of variation of 14.7 per cent. A lead similar to the latter, but more practical in the sense that a shorter anatomic arc is used, is that between point H and a network of points P, A, B, and C. The coefficient of variation of this lead is 16.1 per cent, not significantly larger than that of the previous lead whose arc extends posteriorly to point O. It was then decided that a practical precordial network for the transverse or X vector lead would be the twenty points P, A, B, and C at the five levels, 4 through 8, of Frank's model. Similarly a practical precordial network for a sagittal or Z vector lead would be the twenty-five points, C, D, E, F, and G, at the five levels, 4 through 8. The x, y, and z components of these two networks of points, joined through equal resistors, were then calculated for the 22 dipole location from accurate measurements of Frank's diagrams (Figs. 2,*A*, *B*, and *C* of Ref. 5) of the torso model in terms of image space. The 22 dipole location was chosen because it was very close to, or identical with, the "heart center" found in a number of normal individuals and cardiac patients studied

by several different investigators.[4,6,7] It should be emphasized that, whereas small dipole displacement may produce rather profound changes in the distribution of body surface potentials, the leads to be described inherently possess relative insensitivity to migration of dipole location. Therefore, the accurate location of the electrical heart center, which must have some variation among individuals, is not of paramount importance.

Knowing the x, y, and z components of these two networks in image space, suitable locations for the placement of electrodes which would allow perpendicular X and Z leads to be developed were next considered. Making use of the 22 dipole location it was found that a point* located on the torso between H and I at level 6 was suitable for an electrode against which the potential of the P-A-B-C network was to be measured to form the X lead. Similarly a point* midway between M and N and midway between levels 6 and 6½ was satisfactory for the location of an electrode against which the potential of the C-D-E-F-G network was to be measured to form the Z lead. Finally the Y lead was constructed more simply by making use of the relatively large longitudinal axis of the body. An electrode on point E at level 1 was paired with a network of a point representing the left leg in image space and a point between M and N at level 8. The anatomic connections of these three leads are depicted in Fig. 1,*A* and *B*. Polarities of the leads have been designated in accordance with a recent recommendation.[8] The magnitudes of the vectors are listed in Table I together with the magnitudes of their nonorthogonal components which are also given in terms of "disturbing coefficients"** expressed in per cent. It may be readily seen that these three leads are essentially orthogonal.

TABLE I

	x	y	z
Lead X "Disturbing coefficient"	2.69 = 1.30 − (−1.39)	−0.03 = −0.15 − (−0.12) −1.2%	−0.02 = − 0.27 − (−0.25) −0.8%
Lead Y "Disturbing coefficient"	−0.05 = −0.36 − (−0.31) −1.6%	2.92 = 1.44 − (−1.48)	−0.07 = −0.64 − (−0.57) −2.4%
Lead Z "Disturbing coefficient"	−0.04 = −0.27 − (−0.23) −1.6%	−0.004 = −0.036 − (−0.032) −0.1%	2.70 = 1.10 − (−1.60)

x, y, and z components of leads X, Y, and Z are listed in mv./Ma.-cm. for the human subject with an average resistivity of 1000 ohm-cm.[4,9] The components of the positive and negative poles of these leads are also given in the right-hand member of each equation. The "disturbing coefficients" indicate the degree of variation of the leads from the orthogonal coordinate axes. See text.

For practical clinical purposes the use of network leads formed by multiple electrodes is rather inconvenient. Placement of equal resistors between the terminal and each of the electrodes has been advocated[11] to nullify gross differences in electrode-skin resistance, which would give unequal weight to the individual electrodes of the group. If the possibility of obtaining significantly

***A previous study[2] demonstrated that a small electrode is as efficient as a large electrode or electrode network in these regions for the formation of leads with uniform vectors.**

****This term was first applied by Frank.[10]**

unequal weighting factors is, for the moment, neglected, it is apparent that a solid electrode, conforming to the contour of the torso over the area covered by the mosaic of electrodes of the network, would integrate the potential developed at all points within this area. It is this integrated potential which is highly desirable. In this laboratory, stainless steel foil was first utilized as electrode material; the foil was attached to the chest wall by means of electrode paste and

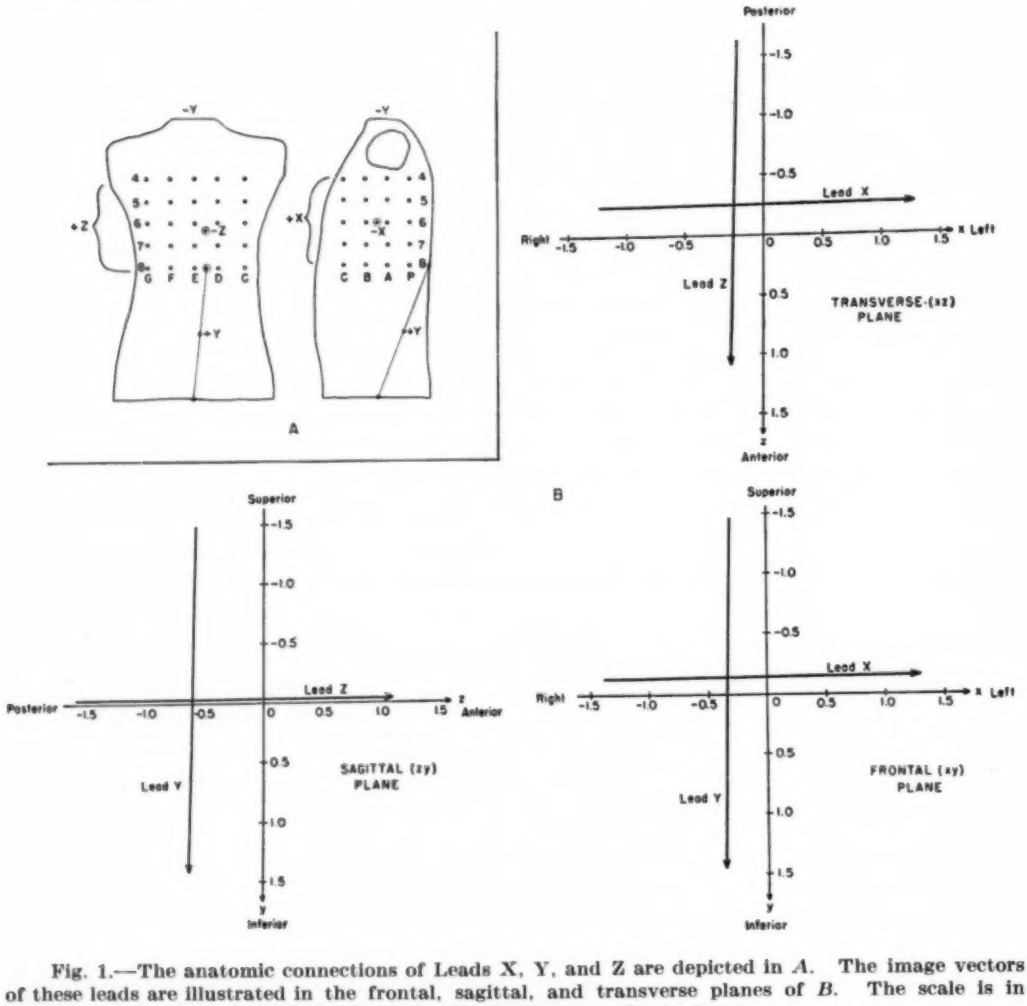


Fig. 1.—The anatomic connections of Leads X, Y, and Z are depicted in *A*. The image vectors of these leads are illustrated in the frontal, sagittal, and transverse planes of *B*. The scale is in mv./Ma.-cm. for a medium with resistivity of 1000 ohm-cm. See text.

rubber straps encircling the chest.[1,2] In recent months a much more practical electrode material has been found to be fine-pore synthetic sponge* having a thickness of ¼ inch and cut to any desired size. When moistened with a solution of sodium chloride** the sponge softens and can be molded to the chest and held in place by rubber straps. This electrode material obviates the expense and the unpleasantness of covering large areas of the chest wall with electrode

*Obtained through the courtesy of E. I. DuPont de Nemours and Company.

**The results obtained with such sponges have been found to be constant with varying concentrations of saline as well as with varying degrees of moistening.

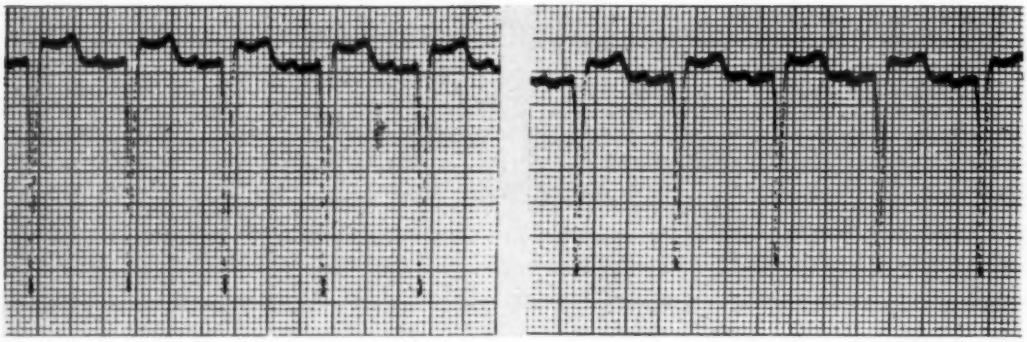
paste. Contact of the lead wire with the moist sponge is best made by means of a crocodile clamp.

The possibility of grossly unequal electrode skin resistances existing beneath various portions of the sponge has been considered. This problem was studied by means of a group of 9 electrodes connected through individual resistors of 10,000 ohms and applied to the chest where columns C, E, and G intersect rows 4, 6, and 8. The potential of such a network terminal was compared with the potential of a saline-moistened sponge electrode covering the same area, each being recorded against the Wilson central terminal. Fig. 2 illustrates a typical result, indicating the close similarity in contour between the tracings obtained with the convenient sponge electrode and the multiple electrode network. The greater magnitude recorded with the sponge electrode should have been anticipated from the fact that the latter effectively averages the potential of the infinite number of points over the area covered. This will be discussed in greater detail later, but it should be pointed out that the 9-electrode network combined with the Wilson central terminal possesses, according to Frank's data for the 22 dipole location, a z component with a magnitude of 1.33 mv./Ma.-cm. Using the same method of arriving at a suitable value for the magnitude of the major components of the leads to be discussed in the next section, the sponge electrode, located in the same area covered by the network combined with the Wilson central terminal, yields a z component with a magnitude of 1.68 mv./Ma.-cm. The ratio 1.33:1.68 is practically identical with the ratio of the magnitudes of the deflections of the two tracings illustrated in Fig. 2.

There would appear to exist the possibility that short-circuiting the high resistance of the skin surface would distort the distribution of electrical potential produced by the heart in such a way that the potentials at areas not covered by the sponge would be significantly altered. This possibility was investigated in various ways. Fig. 3 illustrates Leads CR_2 and CR_6 before and after applying a 19 by 27 cm. saline-containing sponge to the chest between the two precordial electrodes. The lack of any distortion of the leads by this rather massive sponge is readily apparent. Fig. 4,*A* illustrates Lead V_4 taken by means of a Welsh suction electrode.* In Fig. 4,*B* electrode paste has been applied from the clavicles to the sternal margins and from the right to the left midclavicular lines but not in contact with the precordial electrode which continues to record the same electrocardiographic pattern. In Fig. 4,*C* this sheet of paste has been extended laterally to the left midaxillary line, isolating a small ring of dry skin about the precordial electrode. There is again no change in the configuration of Lead V_4. However, when the sheet of paste is brought into contact with the electrode, the recorded voltage diminishes and changes in contour as depicted in Fig. 4,*D*. Thus it is readily apparent that short-circuiting of skin potentials over a very large area of the body surface does not alter the potential developed at an area which is not included with that portion of the skin which is short-circuited.

The excellent reproducibility of leads recorded with a sponge electrode is illustrated in Fig. 5 where the electrode was repeatedly removed, "wrung out,"

*Manufactured by Bowen & Company, Inc., Bethesda, Md.



A. *B.*

Fig. 2.—Comparison of leads recorded against the Wilson central terminal. *A*, Sponge and Wilson central terminal. *B*, Multiple electrodes and Wilson central terminal. The sponge covered the area enclosed between columns C and G and rows 4 and 8 of Frank's model. The multiple electrodes, nine in number, were located at the intersections of columns C, E, and G with rows 4, 6, and 8. See text.

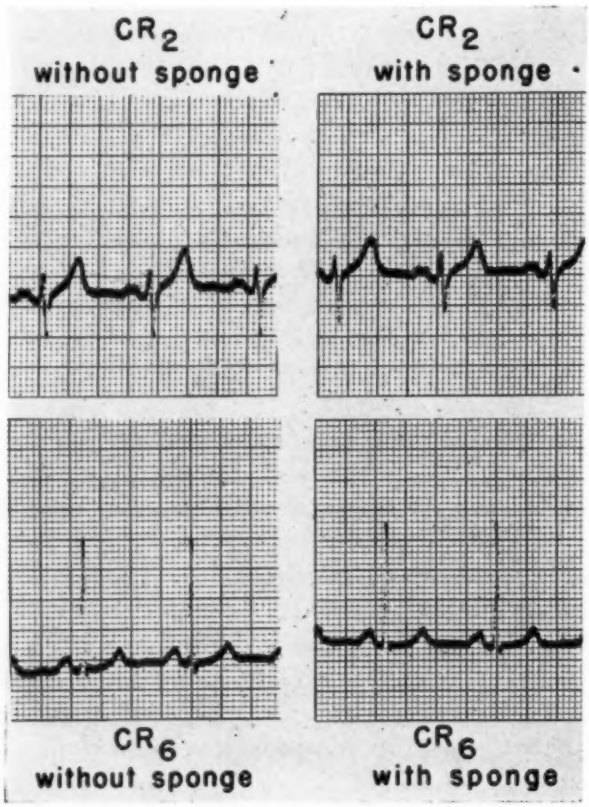


Fig. 3.—Leads CR_2 and CR_6 are essentially unchanged by the placement of a large (19 by 27 cm.) saline-containing sponge on the chest between the two precordial electrodes. See text.

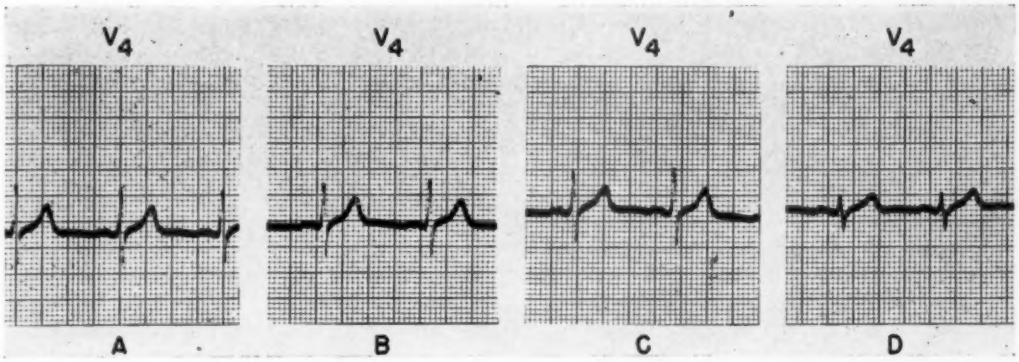


Fig. 4.—Lead V_4 is illustrated in *A*. In *B*, electrode paste covers an area between the right and left midclavicular lines and the clavicles and costal margins. In *C*, the electrode paste has been extended to the left midaxillary line. The illustrations in *B* and *C* demonstrate that the short-circuiting of the skin resistance of an extensive portion of the chest wall produces no change in the electrocardiographic tracing, provided that the sheet of electrode paste is not in actual contact with the precordial electrode. When such contact occurs (*D*), the contour of the tracing is altered. See text.

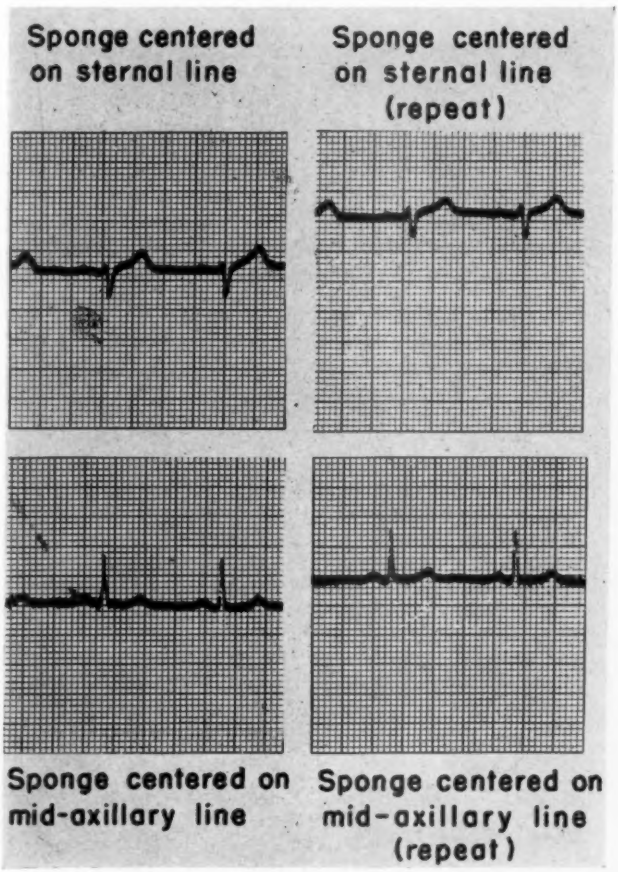


Fig. 5.—The reproducibility of leads recorded with sponge electrodes is illustrated by their removal and replacement as described in the text.

remoistened with grossly varying amounts of saline, and reapplied. The author has also performed calculations, based on Frank's data, which demonstrate that variations in placement of electrodes used for the cube system cause statistically significantly larger errors ($P < .05$) than equivalent variations in placement of the large sponge electrode forming the type of lead under discussion.

PROPOSED REFERENCE FRAME

The reference frame is formed by the use of 7 electrodes with one additional electrode for grounding purposes. Two of the 7 electrodes consist of saline-containing sponge of such a size as to be applicable to the chest in the manner to be described. The remaining 5 electrodes (as well as the ground electrode) may consist of ordinary limb electrodes. I prefer to use the recently described plaster type of limb electrode[12] which is obtainable commercially* and which avoids the inconvenience of electrode paste. The transverse lead, which will hereafter be designated as Lead X, is formed by a limb electrode applied midway between the right anterior axillary and right midaxillary line at the level where the fifth intercostal space intersects the parasternal lines, and a square saline-containing sponge electrode which centers at this same transverse level and extends from the left midclavicular line to the left posterior axillary line. The sagittal or anteroposterior lead, which will subsequently be designated as Lead Z, consists of a limb electrode placed midway between the vertebral and the left scapular lines at a transverse level approximately 1 cm. caudad** to the level of the limb electrode utilized for Lead X, and a square saline-containing sponge electrode centered at the same transverse level as the sponge electrode of Lead X, and extending from (but not quite in contact with) the anterior margin of the latter electrode to a symmetrically identical vertical line on the right anterior chest. For individuals of average body build the sponge electrodes of Leads X and Z may, for practical purposes, be of the same size. These sponge electrodes are held in place by means of three 1-inch rubber straps encircling the chest. The central strap is placed at the level of the limb electrode of Lead X which it supports. This strap is depressed approximately 1 cm. posteriorly to hold in place the limb electrode of Lead Z. The other two rubber straps are placed at the upper and lower margins of the two sponge electrodes, or of the smaller one if they are of unequal size. The levels of the straps, therefore, approximate levels 4, 6, and 8 of Frank's torso.

The longitudinal lead, which will be designated as Lead Y, is formed by a limb electrode placed on the forehead or in the submandibular region and a network of two electrodes, one placed at any convenient location on the left leg and one placed at level 8 (i.e., beneath the lower strap encircling the torso) in the same vertical line upon which the back electrode for Lead Z is located. Since the electrodes at level 8 and on the left leg possess potentials which are usually similar, differences in electrode-skin resistances do not significantly

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*Manufactured under the trade name of "Plastrode" by Bowen & Company, Inc., Bethesda, Md.

**It is likely that these limb electrodes could be placed at the same transverse level without introducing appreciable error; however, strict application of the data listed in Table I suggests the use of the lower level.

affect their average potential. The placement of resistors in this network is, therefore, optional and, in the author's opinion, unnecessary.

If multiple electrode networks were used, as previously described, in place of the sponge electrodes, Table I indicates that the magnitudes of the major component of Leads X, Y, and Z are 2.69, 2.92, and 2.70, respectively. From an examination of Frank's torso diagrams it is rather obvious that increasing the number of points which are symmetrically distributed anatomically over a given area will increase their average potential, and that, if this increase were graphed, the curve should plateau and approach a limit. This may be illustrated by considering the z components of leads formed by the small single electrode on the back in the position previously defined for Lead Z and a variable network of electrodes on the anterior chest. If the latter consists of 10 electrodes placed at the intersection of columns C and G with rows 4 through 8, the z component of such a lead has a magnitude of 2.32 mv./Ma.-cm. If the network is increased by 5 additional electrodes in row E, the magnitude becomes 2.58; and if then 10 additional electrodes are added in rows D and F, the lead becomes that listed in Table I, which has a z magnitude of 2.70 mv./Ma.-cm. If careful measurements are made on Frank's image surface diagrams[5] so as to include electrode points midway between pairs of the five columns, C through G, the number of electrodes is increased to 45, and the magnitude of the z component becomes 2.78 mv./Ma.-cm. Thus, from this progression it becomes obvious that averaging an infinite number of points over an area extending between columns C through G and between rows 4 through 8, as would be produced by a conducting sponge covering this area, would yield a z component which would approach a limit between 2.8 and 2.9 mv./Ma.-cm. It is a justifiable conclusion that a similar sponge placed over an area between columns P through C and between rows 4 through 8 would yield an x component with a magnitude approaching approximately the same limit. The magnitudes of major components of Lead X and of Lead Z are then approximately identical with that of Lead Y. For convenience as well as for maximal accuracy, the author has chosen to select the value of 2.83 or $2\sqrt{2}$ as the magnitude of the major components of all three of the vector leads of this system. (The assumption of an average resistivity of 1000 ohm-cm. is made.[9]) If then a standard current of 1 mv. is adjusted to produce a deflection of $\sqrt{2}$ or 1.414 units, 1 unit of deflection will be equivalent to 2 mv./Ma.-cm.

The three leads of this proposed reference frame may be utilized for either stereovectorcardiography[13] or for multiple-plane spatial vectorcardiography, utilizing the cathode-ray oscilloscope.

SUMMARY

A description is given of the placement of two large saline-containing sponge electrodes and five small conventional electrodes for recording three orthogonal leads which possess relatively uniform vector properties for all portions of the heart. Each of the three leads is assigned a vector magnitude of $2\sqrt{2}$ or 2.83 mv./Ma.-cm. Experimental evidence is cited to justify the substitution of the convenient sponge electrodes for networks of small electrodes joined through resistors.

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GENERAL SYSTEMIC EFFECTS AND ELECTROCARDIOGRAPHIC CHANGES FOLLOWING INJECTIONS OF DIGITALIS GLYCOSIDES INTO THE LATERAL VENTRICLE OF THE BRAIN

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IN EARLIER reported studies by Melville,[1] experiments were presented to show that following injections of ouabain or digitoxin, afferent vagal vasomotor reflex effects arising from the heart appeared to be potentiated. It was, however, not clear to what extent central nervous system effects of the drugs might be involved in this phenomenon. The experiments described in this paper were primarily undertaken with the hope of throwing some light upon this question.

Since the classical observations of Withering,[2] in 1785, it has been well recognized that digitalis administration can induce central nervous system effects in man. With the increasing use of the purified glycosides, there has been a definite increase in the frequency of general systemic toxic complications associated with digitalis therapy (cf. monograph of Lown and Levine[3]). Despite these extensive clinical reports there are relatively few laboratory studies concerning the effects of direct applications of digitalis preparations to the central nervous system.

In 1918, Santesson and Strindberg[4] observed that subdural injections of 1 mg. per kilogram of "Gitalin" (0.1 per cent solution) into the frontal region of the brain of unanesthetized rabbits, induced dyspnea, tremors, miosis, and convulsions, associated with localized muscular weakness and abolition of certain reflexes. These effects were followed by secondary asphyxial convulsions with mydriasis and death due to either respiratory arrest or circulatory failure following an increase in pulse rate.

Rizzolo,[5] in 1929, showed that, following direct application of a 2 per cent strophanthin solution to the cerebral cortex of the unanesthetized dog, there was an initial increase followed by decreased excitability of the cortex. In these experiments the drug was applied for periods of three minutes by means of small squares (1.5 to 2 sq. mm.) of filter paper moistened with the solution. It was also observed that after repeated applications of strophanthin, localized muscular clonus followed by generalized epileptiform convulsions ensued. In view of the high concentrations of the glycosides used in these earlier experiments, the significance of these observations is not too clear.

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Korth, Marx, and Weinberg[6] have also reported that following injections of a relatively small dose (20 μg.) of strophanthin into the lateral ventricle of the brain of unanesthetized dogs, various types of auricular and ventricular tachycardias ensued. This action was inhibited by anesthesia with barbital.

Feldberg and Sherwood[7] have recently described a technique for studying the effects of drugs on the central nervous system, following direct injection of the agents into the lateral ventricle of the brain of the unanesthetized cat. The object of this paper is to present some results obtained in a series of experiments using this technique. In these experiments, both the general systemic effects and the associated electrocardiographic changes following the use of three purified glycosidal preparations of digitalis were investigated. While these experiments were in progress, Weinberg and Haley[8] reported their observations concerning the centrally-mediated effects of strophanthin-k, using a somewhat similar type of cannula inserted into the third ventricle of the brain of dogs.

METHODS

Cats weighing 2.5 to 3 kilograms were used. Pentobarbital sodium 25 mg. per kilogram (intravenously or intraperitoneally) was employed for anesthesia. Sterile technique for the insertion of the cannula was used in all of the earlier experiments but did not prove absolutely essential. Alcohol (70 per cent) and tincture of iodine were applied to the skin of the operative area before and after the operation. Terramycin ointment was also applied locally to the incision. Each cat was injected immediately postoperatively with 250,000 units of penicillin intramuscularly, and the injection repeated six hours later.

In the initial experiments the technique, as described by Feldberg and Sherwood,[7] was followed as closely as possible using the anatomic landmarks suggested by these workers. Owing to the wide variability in the insertion and thickness of the temporal muscles in different cats, satisfactory insertion of the cannula was, however, not always possible. The procedure of these workers was, therefore, somewhat modified. An incision is made over the parietal bone, parallel and close to the midline and extending for 3 to 5 cm. The underlying tissue is cleared away until the junction of the coronal and sagittal sutures is identified. The anatomic landmarks* for the point of trephining the skull are 6 to 6.5 mm. posterior to the coronal suture and 3 to 3.5 mm. from the midline. The skull is drilled with a small electric hand drill inclined towards the midline at an angle of about 30 degrees, and the orifice reamed out; the reaming stops the bleeding promptly and provides the requisite thread for the cannula. The dura is perforated with a 20-gauge needle and the cannula now screwed into place, with a slight inclination towards the midline. While the cannula is firmly held by a spanner, the stylet is removed. Cerebrospinal fluid will then be seen to appear with rhythmic pulsations, if the animal is breathing well; in deeply narcotized cats this may not be readily apparent at the time of the operation, but on recovery fluid may be aspirated through the cannula.

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*The authors are indebted to Drs. Francis L. MacNaughton and Herbert Jasper, Montreal Neurological Institute, for their advice and assistance in establishing these landmarks.

The rubber-tipped cap, through which injections of the drugs are given, is finally screwed on to the cannula.* The incision is closed with sutures or clips. Following removal of these the animal is left to recuperate for a week or ten days and is then ready for use. The same animal can be used again at intervals of no less than seven days.

Three glycosides, lanatoside-C (Cedilanid),** digitoxin (Digitaline Nativelle), and Digoxin,** were selected for this study. In each instance the solutions contained in the ampules were freshly diluted with sterile physiologic saline, so that the dose needed for injection was contained in 0.2 to 0.5 c.c. In several control experiments either physiologic saline alone or a 70 per cent ethyl alcohol solution, diluted with saline as in the case of the glycosidal solutions, was injected. No significant effects followed either of these types of injections.

In most experiments the glycosides (suitably diluted) were injected directly into the lateral ventricle of the brain, with the animal being restrained as little as possible. In a few experiments, by way of comparison, the effects of similar doses were also studied following intravenous injection either into the ear vein or the saphenous vein.

Using needle electrodes, electrocardiograms (Lead II) were taken prior to the injections (marked "Controls" on the figures). The electrocardiograms were repeated at intervals of fifteen minutes thereafter, but at shorter intervals as circumstances required. Thirty-six cats were used in these experiments; some of the animals on repeated occasions.

Since there is considerable evidence that the cardiac action of digitalis might be related to potassium exchange in tissues (see review of Cohen[9] and monograph of Lown and Levine[3]) it was of some interest, in another series of experiments, to investigate the possible influence of simultaneous administration of potassium chloride upon the observed responses to the glycosides, when injected intraventricularly.

RESULTS

1. *General Systemic Changes Following Intraventricular Injections of Glycosides Alone.*—

In general, commencing with minimal doses—1 μg. of each glycoside—the amounts were gradually increased with each succeeding experiment. A dose was soon attained where a definite pattern of reaction was exhibited by the animals. Table I summarizes some examples of the changes observed with increasing doses of each agent.

As can be seen readily with an effective dose of either of the three glycosides, a typical chain of reactions developed. Thus, the cat almost always became subdued, and after a variable interval of time (five to twenty minutes) varying degrees of excitation occurred. Marked dilatation of the pupils, urination, defecation, salivation (at times extremely profuse), and tachypnea were noted, especially with larger doses. As a rule, if the dose of the digitalis preparation was not excessive, the animal recovered, and for a variable number of days exhibited depression, anorexia, and loss of weight.

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*The cannula (with outfit), under the name of "Collison cannula," was obtained from C. F. Palmer Ltd., Brixton, England.

**Kindly supplied by Sandoz & Co., Ltd., and Burroughs Wellcome & Co., Inc., Montreal, respectively.

TABLE I. EFFECTS OF GLYCOSIDES FOLLOWING INJECTIONS INTO THE LATERAL VENTRICLI OF THE BRAIN

	LANTOSIDE-C				DIGOXIN				DIGITOXIN		
Dose (μg.)	5	10	20	50	5	10	20	50	10	60	200
Cat No.	13	15	22	36	9	8	7	24	15	31	31
(a) *Early Effects* Depression (subdued)	+	+	+	+	+	+	+	—	+	—	+
Excitation	—	—	—	—	—	—	—	—	—	+	—
Muscular twitching	—	—	—	+	—	+	—	+	—	—	—
Convulsions (clonic)	—	+	+	+	—	—	—	—	—	—	—
Salivation	—	+	+	++	+	+	+	—	—	—	+
Retching or vomiting	—	—	—	—	—	—	—	—	—	—	—
Defecation	—	—	+	+	—	—	—	—	—	+	+
Urination	—	+	+	—	—	+	+	—	—	—	—
Mydriasis	—	—	—	+	—	+	+	+	—	+	+
Tachypnea	—	—	+	+	—	—	+	+	+	+	+
Died (within 72 hours)	—	—	18 hrs.	3 hrs.	—	—	72 hrs.	35 min.	—	—	48 hrs.
(b) *Later Effects* Anorexia	+	++			+	++			+	—	
Loss of weight	+	++			+	++			+	+	
Recovered	+	+			+	+			+	+	

It is also evident that following smaller doses of 5 to 10 μg. of lanatoside-C or Digoxin, or 10 to 60 μg. of digitoxin, recovery ensued in all cases. However, with higher doses—20 to 50 μg. of either lanatoside-C or Digoxin, and with 200 μg. of digitoxin, the animals died early (within seventy-two hours), from rapid respiratory arrest and/or ventricular fibrillation, as will be shown later.

2. *General Systemic Effects Following Administration of the Glycosides and Potassium Chloride.*—

In Table II are summarized the general systemic responses, observed when potassium was administered in conjunction with the glycosides. In these experiments, the potassium chloride was either injected into the lateral ventricle of the brain simultaneously with the glycoside, or was administered intravenously or intramuscularly, while the glycoside was injected into the lateral ventricle, as stated. One notes again from the table that, following similar doses of the glycosides, the same pattern of responses is observed and these effects are clearly not prevented by administrations of potassium. Indeed, in several of these experiments intense convulsions, salivation, and rapidly fatal tachypnea were observed with lower doses of the glycosides than in similar experiments without potassium administration. In some instances, however, there appeared to be

some protection, especially when higher doses (40 to 60 mg.) of potassium chloride were injected intravenously or intramuscularly.

3. *Electrocardiographic Studies.*—

In the ECG studies, the principal interest was focused on the cardiac rate and the development of arrhythmias, although other findings such as variations in the P-R interval, QRS configuration, and ST-T changes were also noted. Tables III to V summarize these findings, and pertinent tracings illustrating the principal abnormalities which were encountered can be seen in Figs. 1 to 7.

TABLE II. COMBINED EFFECTS OF GLYCOSIDES AND POTASSIUM CHLORIDE FOLLOWING INJECTIONS INTO THE LATERAL VENTRICLE OF THE BRAIN*

	LANATOSIDE-C					DIGOXIN			DIGITOXIN	
Dose (μg.)	5	10	20	40	75	20	50	75	20	75
Potassium Chloride (mg.)	0.25	0.25	1.0	40 I.V.†	60 I.V.‡	0.25	100 I.M.†	60 I.V.§	0.25	60 I.V.§
Cat No.	19	19	17	27	32	28	35	30	29	31
(a) *Early Effects* Depression (subdued)	+	+	+	−	+	+	−	−	+	+
Excitation	+	−	−	+	−	−	+	++	+	−
Muscular twitching	+	+	+	+	+	+	−	−	+	+
Convulsions (chronic)	−	+	++	−	+	+	+	+	−	−
Salivation	−	−	++	+	++	−	+	+	−	−
Retching or vomiting	−	−	−	−	−	−	−	−	−	−
Defecation	−	−	−	−	−	+	+	+	−	+
Urination	−	−	−	−	−	+	+	−	−	−
Mydriasis	−	−	+	−	−	+	+	+	−	−
Tachypnea	+	−	+	+	+	−	−	−	−	+
Died (within 72 hours)	−	−	7 hrs.	−	48 hrs.	6 hrs.	1.5 hrs.	1 hr.	−	−
(b) *Later Effects* Loss of Weight, anorexia	+	+		+					+	+
Recovered	+	+		+					+	+

*In each experiment the potassium chloride was given with or immediately following the glycoside.
†In two divided doses at 15-minute intervals. I.V. = intravenously, I.M. = intramuscularly.
‡In three divided doses at 15-minute intervals.
§In three divided doses (15 minutes apart).

In general, the influence on the cardiac rate was quite variable; the type of glycoside or the dosage apparently did not play an important role. Frequently, an initial bradycardia preceded a tachycardia and conversely. Various types of arrhythmias were, however, observed and constituted much more concrete and definite changes.

TABLE III. ECG EFFECTS OF LANATOSIDE-C (CEDILANID) AND INFLUENCE OF POTASSIUM

Cat No.	13	15	22	36	19	20	21	19	27	32
Cedilanid (μg.)	5	10	20	50	10	20	20	5	40	75
KCl (mg.)	–	–	–	–	.25	.25	.25	.25	40 I.V.	60 I.V.
Rate/min.	< >	<	<	>	> <	>	<	>	< >	>
P-R interval	>	–	–	>	>	–	–	–	–	–
P wave	–	>	<	>	–	>	–	–	–	–
QRS complex	–	<	–	<	Deep S	Deep S	–	–	<	Deep S
S-T interval	El.	El.	El.	El.	–	–	Sag.	–	–	–
T wave	Up.	Dip.	Fl.	Dip.	–	>	Inv.	–	Fl. Inv.	Fl.
Arrhythmia	–	–	+	–	–	+	+	–	+	–
Time of appearance of maximal effects (min.)	30	30	45	30	45	30	15	15	15-60	30

El. = elevated, Sag. = sagging, Up. = upright, Dip. = diphasic, Fl. = flattened, and Inv. = inverted.

TABLE IV. ECG EFFECTS OF DIGOXIN AND INFLUENCE OF POTASSIUM

Cat No.	9	26	24	28	25	30	33	27	35	36
Digoxin (μg.)	1	20	50	20	50	75	25	50	50	25
KCl (mg.)	–	–	–	.25	.25	60 I.V.	40 I.M.	60 I.M.	100 I.M.	100 I.M.
Rate/min.	>	<	> <	>	> <	< >	>	< >	> <	< >
P-R interval	–	–	>	–	–	–	–	–	–	–
P wave	–	–	>	–	–	–	–	–	–	–
QRS complex	> <	–	<	Deep S	–	–	–	<	–	<
S-T interval	–	–	–	Sag.	El.	–	Sag.	–	–	
T wave	<	–	<	Dip.	Inv.	Inv.	Inv.	Inv.	–	Dip.
Arrhythmia	–	–	++	–	+++	+++	+++	+++	+++	
Time of appearance of maximal effects (min.)	30	15	30	30	30	15	60	60	15-60	30

El. = elevated, Sag. = sagging, Up. = upright, Fl. = flattened, Inv. = inverted, and Dip. = diphasic.

TABLE V. ECG EFFECTS OF DIGITOXIN (DIGITALINE NATIVELLE) AND INFLUENCE OF POTASSIUM

Cat No.	13	12	9	15	27	31	31	34	29	31
Digitoxin (μg.)	5	5	5	10	20	60	200	200	20	75
KCl (mg.)	–	–	–	–	–	–	–	–	.25	60 I.M.
Rate/min.	>	< >	< >	< >	>	>	>	>	>	< >
P-R interval	–	–	–	–	–	–	–	–	–	–
P wave	–	>	–	–	<	<	–	>	>	>
QRS complex	–	–	>	>	R > S >	–	–		R > R <	S >
S-T interval	El.	Sag.	–	–	Sag.	El.	El.	El.	Sag.	Sag.
T wave	–	–	>	>	<	Dip.	Inv.	Inv.	< >	Inv.
Arrhythmia	–	–	–	–	–	–	–	++	–	–
Time of appearance of maximal effects (min.)	30	30	15	30	30	45	60	5	30	45

El. = elevated, Sag. = sagging, Up. = upright, Dip. = diphasic, Fl. = flattened, and Inv. = inverted.

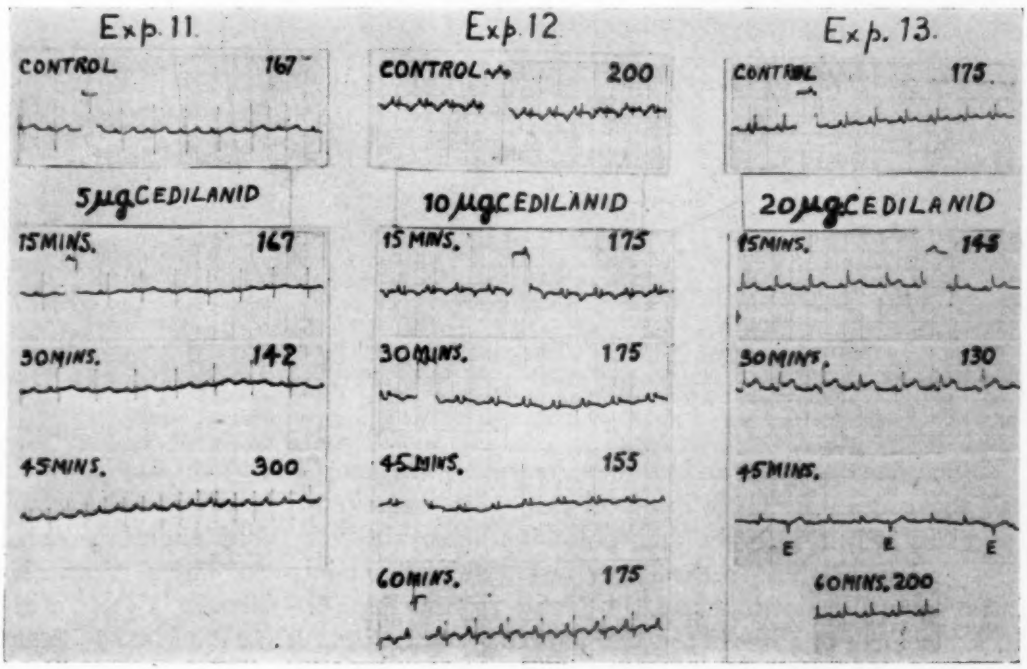

Fig. 1.—Effects of lanatoside-C (Cedilanid). Electrocardiograms (Lead II) taken as marked—the heart rates per minute are also shown. *Exp. 11:* cat, female, 2.5 Kg.; *Exp. 12:* cat, female, 3.4 Kg.; *Exp. 13:* cat, female, 2.65 Kg. *E* = ectopic beats. See text.

A dose of 20 μg. of lanatoside-C alone produced an arrhythmia chiefly in the form of ectopic beats (Fig. 1, Exp. 13). Similarly, with a dose of 50 μg. of Digoxin alone, a pronounced effect could be elicited (Fig. 2, Exp. 3): continuous strip (Fig. 4,*A* to *C*) shows rhythmic variations due to beats from various foci. While it appeared that the animals tolerated digitoxin best, and even doses as high as 200 μg. produced at times no appreciable effect (Table V, Cat No. 31), in one instance (Fig. 3, Exp. 25) following a similar injection there was a rapid onset of arrhythmia which terminated fatally.

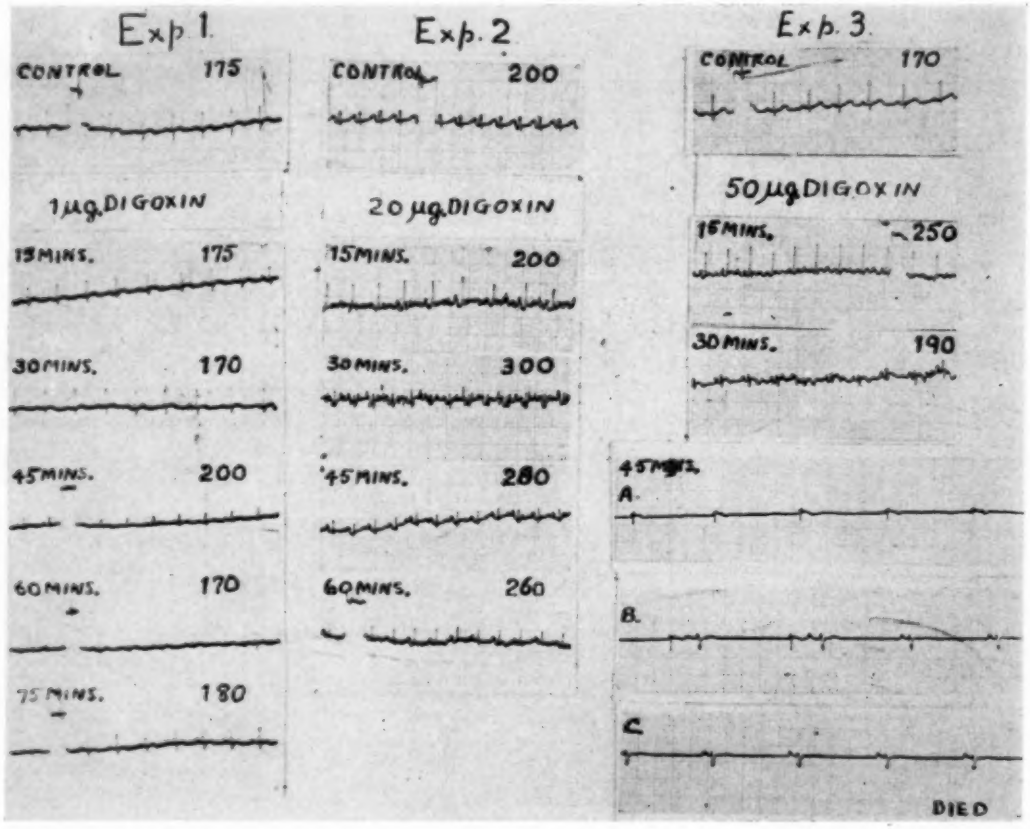

Fig. 2.—Effects of Digoxin. Electrocardiograms (Lead II) taken as marked—the heart rates per minute are also shown. *Exp. 1:* cat, male, 2.3 Kg.; *Exp. 2:* cat, male, 2.4 Kg.; *Exp. 3:* cat, male, 2.95 Kg. *A*, *B*, and *C* are continuous records. See text.

The most striking arrhythmias, however, were noted in those cats in which the glycosides were given in association with potassium (Figs. 4, 5, and 6), and especially when Digoxin and potassium chloride were used simultaneously, irrespective of whether the latter was administered into the lateral ventricle, intravenously or intramuscularly (Table IV and Fig. 5). All cats injected with 50 μg. or more of Digoxin showed marked arrhythmias. Thus Cat No. 30 (Table IV) showed A-V dissociation which set in within fifteen minutes, QRS complexes with markedly inverted T waves, only occasionally discernible P waves, and eventually cardiac standstill. However, even following a dose of 25 μg. of

Digoxin Cat No. 33 (Table IV) showed the development of ventricular fibrillation in sixty minutes, in contrast to Cat No. 26 (Table IV) which showed no arrhythmia and survived following a dose of 20 μg. It can also be seen from Fig. 5, Exp. 5 (continuous strip *A* to *D*) that after 50 μg. of Digoxin with added potassium, there occurred within sixty minutes definite A-V dissociation, occasional ectopic beats, and finally auricular standstill with sporadic ventricular beats until cessation of cardiac activity. Experiment 9 (same figure) shows again another example in which 100 mg. of potassium chloride was injected intramuscularly; there were marked arrhythmias developing as early as fifteen minutes and characterized by multifocal beats and runs of atrial paroxysmal tachycardia, and in one hour an abrupt change to bradycardia with eventual ventricular fibrillation.

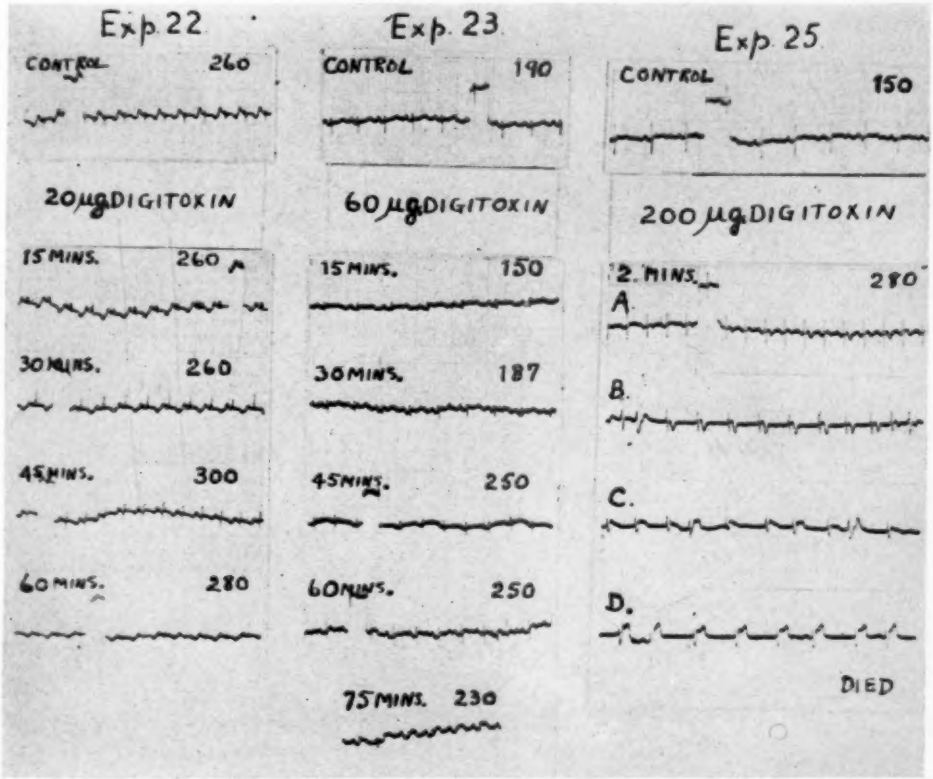

Fig. 3.—Effects of digitoxin (Digitaline Nativelle). Electrocardiograms (Lead II) taken as marked —the heart rates per minute are also shown. *Exp. 22:* cat, male, 2.95 Kg.; *Exp. 23:* cat, male 2.05 Kg.; *Exp. 25:* cat, female, 2.05 Kg. *A*, *B*, *C*, and *D* are continuous records. See text.

In addition, alterations in the P waves and P-R intervals were occasionally noted. S-T deviations from the isoelectric line and flattening or inversion of T waves were often observed in conjunction with alterations in the rate. Alterations in the configuration of the QRS were noted sporadically.

In several of the above experiments, the associated injections of potassium chloride frequently precipitated muscular twitching and convulsions even following small doses of the glycoside. These were reflected in the tracings as

artefacts marked "tremors," as can be seen in Fig. 5 (Exp. 4) following injections of 20 μg. of Digoxin with 250 μg. of potassium chloride. Figs. 4 and 6 also show examples of exaggerated motor activity.

In contrast to the above findings, as shown in Fig. 7 following intravenous injection of a dose as high as 50 μg. of Digoxin, there were no significant changes in the electrocardiograms (Exp. 28). Similarly, neither intraventricular (500 μg.) nor intramuscular (150 mg.) injections of potassium chloride led to any noteworthy disturbances (Exp. 30 and 32). Similar results were obtained in several other experiments. It is evident, therefore, that systemic absorption from the lateral ventricle of the relatively small quantities of both the glycosides and potassium chloride, as employed in the experiments described above, could not account for the electrocardiographic and other changes observed.

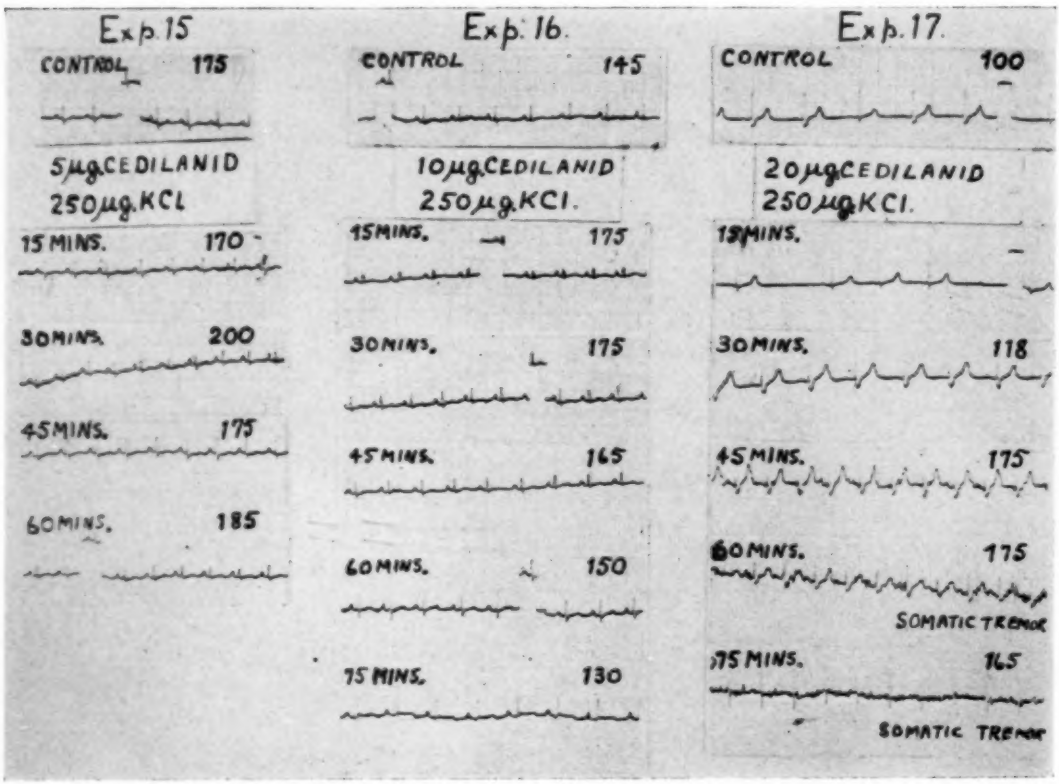

Fig. 4.—Effects of lanatoside-C (Cedilanid) and potassium chloride. Electrocardiograms (Lead II) taken as marked—the heart rates per minute are also shown. *Exp. 15:* cat, male, 2.35 Kg.; *Exp. 16:* cat, male, 2.7 Kg.; *Exp. 17:* cat, male, 2.9 Kg. Artefacts on lower records. See text.

DISCUSSION

With an appropriate dose of any of the glycosides used in this study, a definite pattern of reaction was always obtained. The number of symptoms exhibited by the cat, and their intensity and rapidity of appearance, are apparently related directly to the size of the dose of the preparation used. No such results were obtained with equivalent volumes of physiologic saline injected

into the lateral ventricle, nor was any effect elicited by the injection of alcohol in small amounts equivalent to those present in the commerical glycoside solutions used in our experiments. Furthermore, in all the cats which survived the acute experiments, anorexia, depression, and loss of weight were constant and pronounced features. The duration of these effects and their intensity were also directly dependent on the amount of digitalis used in the experiments. All of these different factors would seem to point to the observed effects as due to some specific central nervous system action of the glycosides. It is of special interest to note that at no time was vomiting observed as a reaction.

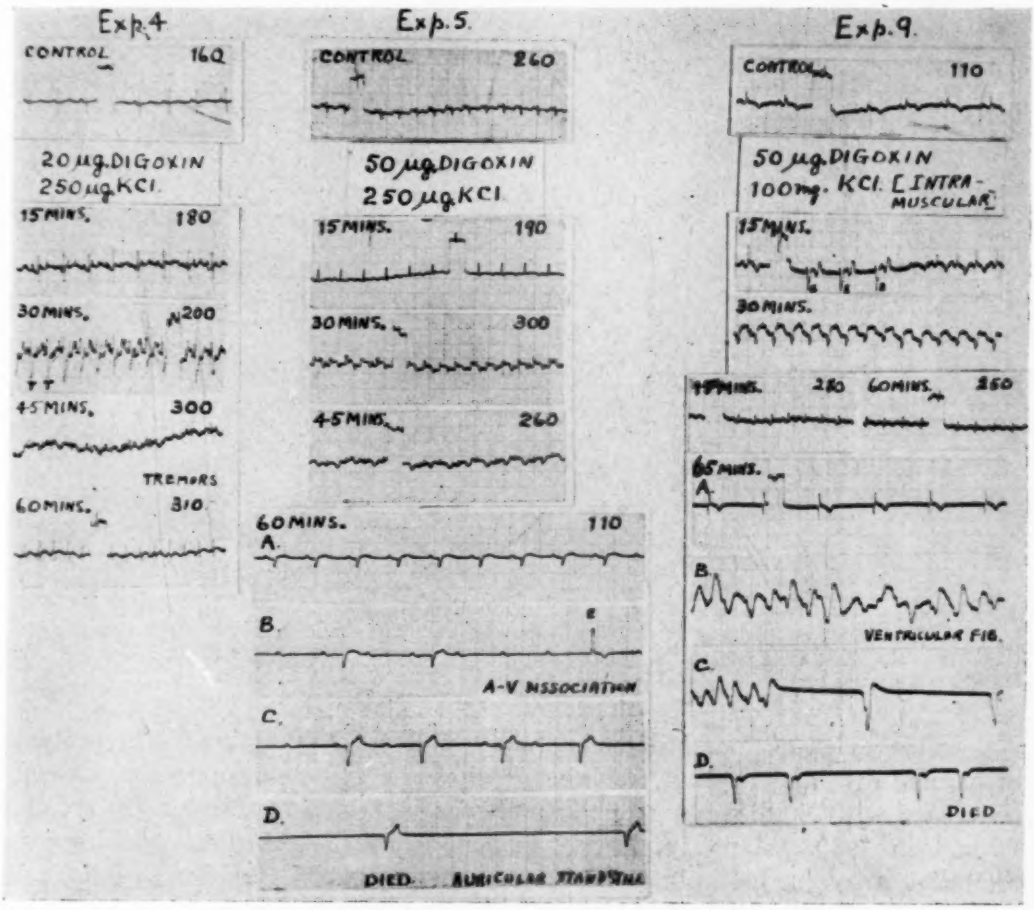

Fig. 5.—Effects of Digoxin and potassium chloride. Electrocardiograms (Lead II) taken as marked —the heart rates per minute are also shown. *Exp. 4:* cat, female, 2.5 Kg.; *Exp. 5:* cat, female, 2.6 Kg.; *Exp. 9:* cat, female, 2.45 Kg. *A*, *B*, *C*, and *D* are continuous records. *E* = ectopic beats. See text.

The effects of injections of the glycosides into the lateral ventricle on the cardiac rate and rhythm were rather surprising. Doses producing cardiac effects as shown were certainly too small to produce similar effects when used intravenously. These observations would, however, be in accord with some of the clinical and earlier experimental observations referred to above, and would

certainly suggest that digitalis may have circulatory effects which are noncardiac in origin. Weinberg and Haley[8] have also reported somewhat similar observations on dogs. While the immediate reactions observed would seem to be due to some form of "autonomic discharge" as suggested by these authors, the exact pathways involved are still rather obscure, and their precise neurologic localization would require further study.

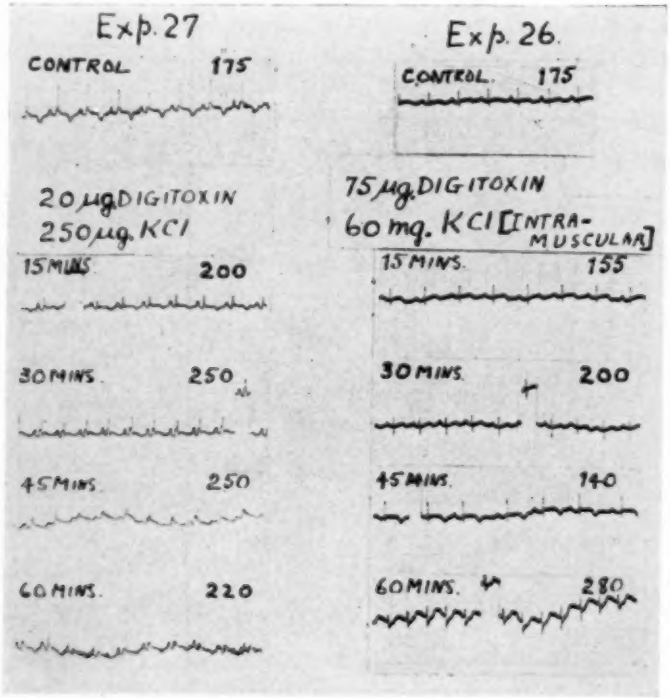

Fig. 6.—Effects of digitoxin (Digitaline Nativelle) and potassium chloride. Electrocardiograms (Lead II)—the heart rates per minute are also shown. *Exp. 26:* **cat, female, 2.55 Kg.;** *Exp. 27:* **cat, male, 2.5 Kg. See text.**

In his review of the relationship of hypothalamic dysfunction to the problem of cardiac rate and rhythm, Weinberg[10] cites the principal anatomic pathway concerned with these types of arrhythmias as identified by Beattie, Brow, and Long,[11] in 1930. Similarly, Hess,[12] in his precise localization, demonstrated numerous areas in the brain which were concerned with regulation of pulse rate and blood pressure. Whether or not the cardiac changes described in this paper are mediated through these possible pathways is not certain.

While studying the role of potassium in the cerebrospinal fluid, Devos,[13a,13b] in 1951, found that an excess of potassium in the cerebral ventricles produces a tachycardia, preceded by transitory bradycardia. From his experiments he also concluded that some nervous structures of the third ventricle have a direct influence on the heart rate. While the effects of simultaneous potassium and digitalis administrations in these studies are somewhat equivocal, it is clear that such injections of potassium chloride do not protect from the effects of the glycosides, and in almost every instance hastened the precipitation of violent

motor convulsive seizures and death from either respiratory arrest or ventricular fibrillation, or both. This could conceivably be due only to additive central nervous system actions of the two agents.

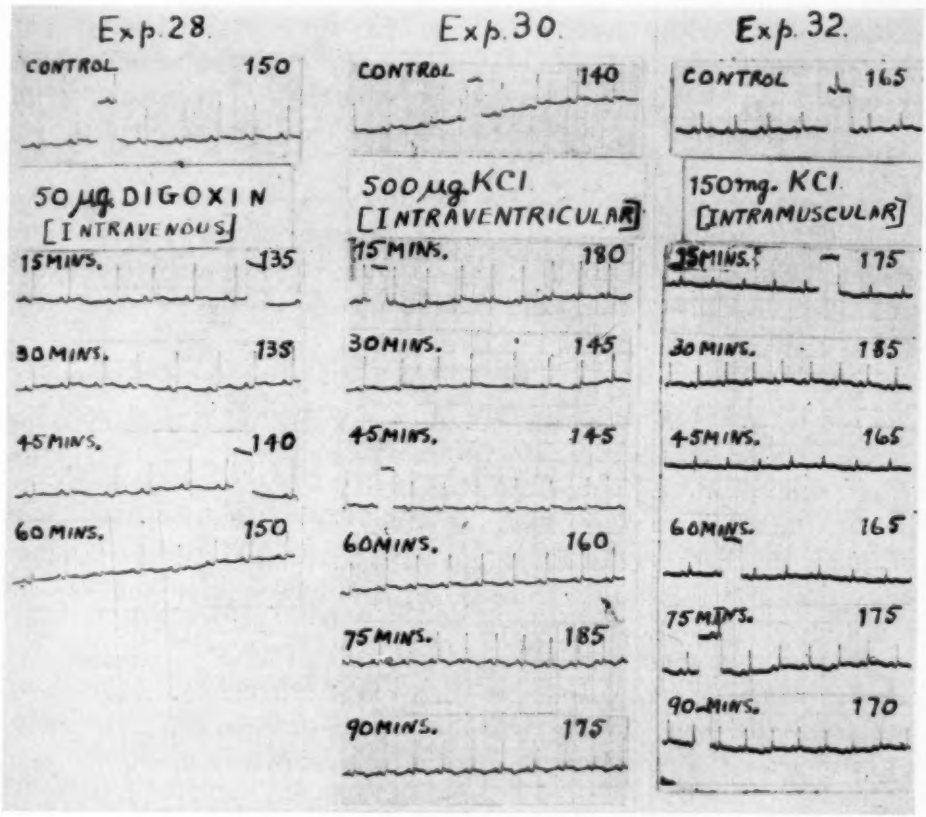

Fig. 7.—Effects of intravenous Digoxin, intraventricular potassium chloride, and intramuscular potassium chloride. *Exp. 28:* cat, male, 2.05 Kg.; *Exp. 30:* cat, male, 2.6 Kg.; *Exp. 32:* cat, male, 2.55 Kg. See text.

In connection with the findings reported, it is of interest to note that Konzett and Rothlin[14] and Perry and Reinert[15] have more recently reported that the cardiac glycosides can potentiate the stimulant action of acetylcholine on ganglionic transmission in the perfused superior cervical ganglion of the cat. The latter authors have also shown that this effect of the glycosides cannot occur in the absence of potassium ions, that is during perfusion with Locke's solution lacking in potassium. It was, therefore, concluded that the glycosides render ganglion cells more permeable to potassium ions. In addition, Cattell[16] has shown that in striated muscle the glycosides increase the permeability of the cell membrane to potassium; and Scarinci[17] has observed that the positive inotropic action of digitalis on the isolated frog heart preparation is dependent on the presence of potassium in the perfusing fluid. It is conceivable, therefore, that the above-described central nervous system effects of the glycosides and their potentiation by potassium might be due to similar type of action on central synaptic transmission involving acetylcholine mediation. This hypothesis, however, requires further study.

Irrespective of the mechanism involved, the data suggest two points which might be of practical therapeutic importance; namely (1) that the general symptoms of digitalis overdosage and various associated cardiac arrhythmias can result from the presence of relatively low concentrations of the glycosides within the central nervous system, and (2) that these effects are not antagonized by potassium. Indeed, this latter effect might explain some of the contradictory reports in the literature regarding the efficacy of potassium administration in the treatment of digitalis overdosage. It is conceivable that the direct myocardial depressant action of potassium might antagonize direct cardiac actions of the glycosides, and to some extent this was observed following injections of larger doses of potassium chloride. However, as is well known, both hypopotassemia and hyperpotassemia can induce cardiac arrhythmias. It is therefore clear that the relationship of potassium to cardiac function requires further study.

SUMMARY

The general systemic responses and electrocardiographic changes following direct injections of lanatoside-C (Cedilanid), Digoxin, and digitoxin into the lateral ventricle of unanesthetized cats are described, and the influence of potassium chloride administrations upon these responses studied. It was observed that relatively small doses (5 to 200 μg.) of these glycosides induce predominantly central nervous system excitation associated with cardiac arrhythmias. These effects are in general not antagonized, but rather accentuated by potassium. It is postulated that these actions might be due to effects on central synaptic transmission involving acetylcholine. These observations might also offer some explanation of the contradictory observations in the literature regarding the efficacy or otherwise of potassium therapy in digitalis overdosage. The problem is being further investigated.

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CURRENT INDICATIONS FOR THE SURGICAL CORRECTION OF MITRAL STENOSIS

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DISABLING mitral stenosis can generally be relieved by good valvuloplasty. The responsibility of the physician in this situation was outlined years ago.[1] By defining surgical risk at various points in the life cycle of mitral stenosis it became apparent that a time could be selected when the risk of operation was low and chances of rehabilitation great. Recent improvement in diagnosis, medical and surgical management have increased this responsibility.[2]

Three stages of increasing responsibility have evolved. The first was that trial period in which some salvage was extended terminal patients. The second, emphasized earlier surgical intervention for patients (Group III) with "pure" mitral stenosis where surgical risk is low and chances of rehabilitation great. Conversely this stage points up the dereliction of duty to patients when they are "followed on medical treatment" as they disintegrate into the late, preterminal phase. The third stage extends surgery to multivalvular problems.

Our first 500 patients who had valvuloplasty for mitral stenosis are being used as a pilot study. This group has been followed for a mean period of more than three years. The results have been reported.[3,4] Our clinical classification of mitral stenosis should not be confused with the American Heart Classification of Cardiac Disease even though there are certain similarities. The criteria for our four groups are shown in Table I. We have preferred to operate on patients

TABLE I. CLINICAL CLASSIFICATION OF PATIENTS WITH MITRAL STENOSIS

Group 1.—Benign:	Murmur only—no symptoms
Group 2.—Handicapped:	Murmur plus symptoms which are static
Group 3.—Hazardous:	Murmur plus progressive symptoms with evidence of right ventricular failure that responds to therapy
Group 4.—Terminal:	Murmur, progressive symptoms, and irreversible congestive failure

in Group 3 because these individuals gain the most at least risk. Because of

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the small number of Group 2 patients, they are included with those in Group 3 in the analysis. Table II shows the operative mortality in the first 1,000 patients in these categories. Following the developmental stage (the first hundred operations) the mortality rate in Group 3 dropped precipitously and has remained low. Currently this Group 3 mortality is less than 1 per cent. This is comparable to or better than that of major abdominal surgery. In the Group 4 patients (those in irreversible congestive failure), however, the mortality rate has remained between 20 and 25 per cent. It must be realized, however, that many patients are now referred for surgery who would not have been considered formerly. Thus, the composition of Group 4 has deteriorated over the years without a concomitant increase in the mortality rate. The net effect is obviously a gain.

TABLE II. MORTALITY OF FIRST 1,000 PATIENTS UNDERGOING MITRAL VALVULOPLASTY

PATIENT NUMBER	GROUPS 2 AND 3 (%)	GROUP 4 (%)
1–100	14	32
101–500	3.5	24
501–1000	0.6	20

One should view this Group 4 mortality of 20 to 25 per cent in proper perspective. In nineteen such patients who refused surgery early in our experience, the mortality without operation was 89 per cent within six months. These terminal patients have been variously designated as in "the malignant phase," "the dying phase," etc. We have never accepted severity of disability nor irreversibility of congestive failure as contraindications to operation. Even with such a policy, however, an 89 per cent mortality has been changed to an 80 per cent salvage rate. This consistent experience emphasizes the value of surgery even after the most favorable time for operation has passed. The significant fact, however, is that the mortality is multiplied twenty fold when the patient is allowed to deteriorate from Group 3 to Group 4.

In this extensive experience with more than 1,000 operations on the mitral valve, interest should focus on the late as well as the early postoperative results. Here again we look to the three-year follow-up study.[3] In the combined Groups 2 and 3, 89 per cent are improved, and 56 per cent are leading essentially normal lives. These figures include the very first operations. Similar scrutiny of the second 500 patients promises even better results. Techniques for converting the stenotic orifices into adequately functioning valves have inevitably undergone substantial improvement. The criteria for a satisfactory opening have become much more stringent. For example, no postvalvuloplasty orifice which is estimated to be less than 3.5 square centimeters in area is now considered acceptable.*

*Experience with a series of this size should result in improvement in results. That such improvement rather than repetition of error has occurred is due in no small part to Dr. Laurence B. Ellis and his colleagues who have meticulously followed the patients after operation. Their correlation of the degree of improvement with accurate drawings of the valve made by the surgeon at the time of operation has been invaluable.

Low risk and a high incidence of significant improvement following mitral valvuloplasty have thus been established. However, one may still ask, "If the patient is responding reasonably well to medical management, why should we operate?" Love and Levine[5] have clarified this. In their report on 164 patients with mitral stenosis followed in a cardiac clinic, 13 per cent survived nine or more years after the first signs of congestive failure or auricular fibrillation. This study warns us that medical management carried an 87 per cent mortality over this period. It is unlikely that those who died lived comfortably until their last day. Indeed survival should not be the only criterion by which results are judged. How many of them were able to perform as adequate individuals, either maintaining a job and supporting themselves or taking care of their families and housework? How many were disabled by arterial embolization to brain or body? Finally, one must ask how cruel a burden was imposed by the dyspnea, palpitation, hemoptysis, paroxysmal noctural dyspnea, recurrent pulmonary infections, and/or all the other complications of rheumatic mitral stenosis in those who died as well as in those who survived. Against this background one soon appreciates the inadequacy of survival as the statistical dimension.

A dispassionate consideration of these sharply contrasting mortality and rehabilitation rates can only lead one to the conclusion that it is a dereliction of duty not to bring the patient to surgery before permanent irreversible damage to lungs, liver, and myocardium has been done. If this point is conceded, how early in the disease should surgical correction be considered? With the mortality rate in experienced hands remaining consistently in the neighborhood of 1 per cent in early favorable cases, it becomes apparent that the diagnosis of symptomatic mitral stenosis should be enough to make the physician consider operative correction. There is very little argument about the proper treatment for patent ductus arteriosus, yet the surgical risk is no less. This analogy is not quite fair in view of the variation of quality in the surgical correction of mitral stenosis as contrasted with the all-or-none nature of ductus closure. However, there is a proper point to be made. We have been more conservative than others in recommending operation for mitral stenosis, but the low risk now demands a more liberal attitude.

At the present time, the following factors strongly point to the need for surgical intervention in a patient with pure mitral stenosis:

1. *Episodes of congestive failure* characterized by such ominous features as dyspnea, liver enlargement, peripheral edema and râles. Such patients can generally be brought out of failure with bed rest, digitalis, and diuretics. However, the development of congestive failure heralds the onset of a phase that is likely to be progressive. There exists in addition the threat of fatal pulmonary edema or pulmonary or peripheral embolization. Procrastination at this point only exposes the patient to unnecessary medical risk and subsequently to a higher operative risk.

The recurrent episodes of respiratory infection, or so-called "virus pneumonias" suffered by these unfortunate patients, are usually the result of infected pulmonary edema. They respond to antibiotics, bed rest, and oxygen, with or without supplementary digitalis and diuretics. The elimination of these variously labeled attacks following relief of the stenosis suggests their true nature.

2. *Radiologic evidence of pulmonary hypertension* is of great importance. It is manifested by pulmonary artery and right ventricular enlargement which may occur in the absence of significant increase in the transverse diameter of the cardiac silhouette in the conventional postero-

anterior film. Even in the well-compensated patient this indicates that the mitral orifice has become critically narrowed and that pulmonary hypertension is imposing a load on the lesser circulation and right heart that may lead to irreversible changes.

Another clue to critical narrowing of the mitral valve is the appearance of marked pulmonary vascular congestion which may in time be associated with hemosiderosis of the lungs. Such a patient may have very little dyspnea or disability for, as Dexter pointed out, a high degree of pulmonary vascular disease secondary to mitral valvular obstruction may protect the patient from dyspnea but place a great load on the right ventricle. One should respect these important radiologic warnings for such a patient can pass rapidly from a good-risk category to a stage of irreversible congestive failure when his right ventricle decompensates and dilates with ensuing tricuspid insufficiency.

3. *Electrocardiographic evidence of right ventricular hypertrophy*, "strain," or right bundle-branch block is another sensitive index that a critical load is being thrown on the right side of the heart. This may be absent initially, but its appearance often heralds progressive deterioration.

4. *Auricular fibrillation*, even transient in character, forbodes trouble. Arterial emboli are the greatest source of mortality and morbidity in mitral stenosis surgery, and the causal relationships between auricular fibrillation, clot, and embolization are obvious. Commonly the patient with mitral stenosis has episodic auricular fibrillation that reverts spontaneously or may be reverted with quinidine. Within a few months of its first appearance, however, auricular fibrillation may become permanent, and this event is often the turning point leading to a progressively complicated course.

It should be mentioned here that attempts to revert patients to normal rhythm before operation are unreasonable. There is a definite risk of embolization coincident with reversion, and furthermore, such patients will almost inevitably develop auricular fibrillation immediately after surgery anyway. It is more reasonable to flush out any auricular clot and correct the stenosis first; then soon after operation reversion can be attempted. Maintenance of a normal rhythm is then more likely. If reversion is unsuccessful, further attempts should be made one, six, and twelve months after operation. Those who revert are maintained on quinidine.

5. *Difficulty with sexual intercourse* is a problem of vast importance for the patient with mitral stenosis. It may constitute the most significant limitation but escape detection in routine history taking. The mechanism by which tachycardia leads to dyspnea and pulmonary congestion because of diminished diastolic filling time has been discussed elsewhere. Difficult or impossible sexual compatability may readily lead to strained marital relationships and often to separation and divorce. It must be emphasized that this information is not often volunteered, but that careful and sympathetic questioning will demonstrate how commonly this difficulty is a significant factor in the patient's life.

6. *Repeated arterial embolization* is now regarded as an indication for mitral valvuloplasty. Emboli are responsible for a significant medical mortality and morbidity from mitral stenosis. If not fatal, they may result in permanent hemiparesis, peripheral arterial insufficiency, or loss of limb. During a mean postoperative follow-up period of two years (800 patient-years of observation) only five suffered emboli in contrast to seventy-nine of the group who had had emboli before operation. Operation therefore appears to decrease substantially the risk of embolization. Current operative procedures should give an even greater margin of protection because of more consistently adequate relief of stenosis and complete auricular appendicectomy.

7. *Severe symptoms from mitral stenosis in pregnancy* may constitute an indication for valvuloplasty, particularly for those women who, because of religious belief or personal preference, are unwilling to accept interruption. Women with mitral stenosis may go through one or more pregnancies without trouble. As the narrowing of the valve becomes critical, however, they may experience increasing difficulty with each pregnancy and eventually the congestive symptoms may threaten life. The symptoms experienced because of increased demand for cardiac output during gestation are dyspnea, pulmonary edema, hemoptysis, or right heart failure. Valvuloplasty may be offered to such individuals with assurance if certain criteria based on the experince to be described are observed. *First*, the diagnosis of mitral stenosis must have been established before pregnancy. The increased blood flow during gestation may produce murmurs that can confuse the most experienced cardiologist. Although pregnancy seems to confer some degree of

protection it must be recognized as well that progressive difficulty at this time may be caused by a recrudescence of rheumatic activity. Therefore a prior diagnosis is mandatory. *Second*, the pregnancy should be carried beyond the second month before operation is undertaken in order to avoid a period of anoxia that might produce congenital anomalies in the fetus. *Third*, the valvuloplasty preferably should be performed before it can add to the burden of peak load of the sixth, seventh, and eighth months. *Fourth*, the patient must be maintained on a strict cardiac regimen with marked reduction in activity during the remainder of the pregnancy in order to limit the myocardial burden. *Fifth*, unless Caesarian section is specifically indicated by some factor such as disproportion, the delivery should be by pelvic route with low forceps assistance.

In twenty-two patients who have had mitral valvuloplasty during pregnancy there have been three deaths. All of these were due to factors unrelated to the pregnant state (cerebral embolus, ventricular fibrillation on the operating table, and rheumatic carditis of overwhelming degree occurring two months after the cardiac procedure and following shortly upon interruption of the pregnancy). The remainder of these patients have done well, continuing to term, delivering normally, and showing progressive improvement afterward. One patient delivered twins without difficulty five months after valvuloplasty.

COMPLICATING FACTORS

In the earlier report[1] on the indications for mitral valvuloplasty certain relative contraindications were mentioned. Age over 50 was one of these, but this has diminished progressively in importance. More than 100 patients past 50 have now had mitral valvuloplasty; the oldest patient was 70. Results in these individuals are comparable to those in younger age groups.

It should be emphasized that "age is a function of the proximity to the end of life, not the distance from the beginning." Thus the 30-year-old terminal patient may be "older" than the well-preserved one at 65. Age per se, therefore, must not preclude operation.

One must avoid, if possible, the pitfall presented by the patient with minimal valvular changes giving rise to auscultatory evidence of stenosis, whose significant cardiac symptoms are in fact due to coronary insufficiency. In this older age group, the highly important electrocardiographic evidence of right ventricular hypertrophy is often absent, even when significant stenosis exists. However, if other criteria are present, one should not hesitate to proceed with surgery. At times it may be necessary to explore such a patient so that the correctible lesion (mitral stenosis) is not overlooked. The results of operation in the sixth and seventh decades have been as gratifying as those in younger patients and are being reported elsewhere.

Auricular fibrillation was mentioned in the earlier report as a "relative contraindication." Fifty-four per cent of this entire series and 84 per cent of those in Group 4 were fibrillating at the time of operation. Thus fibrillation is never considered a contraindication. Pursuant to this point, improved methods of managing auricular clot, including flushing and aspiration, have almost eliminated embolus from this source.

Moderate mitral insufficiency does not preclude valvuloplasty for associated predominant stenosis. The clinical differentiation of these two conditions is often difficult but has been greatly clarified with increasing experience. This is considered in another communication.[6] It should also be noted that left heart catheterization by the percutaneous method often helps clarify the nature of the valvular disease.

Ellis has found in his follow-up of patients after mitral valvuloplasty that 82 per cent of patients who had mild to moderate regurgitation at the time of operation were improved.[4] Even when the degree of regurgitation was described as moderate to marked by the operator, 63 per cent were benefitted. Significant insufficiency obviously influences the result, but it is important to note that even when present the majority of these individuals did well. It is particularly important to bear this fact in mind in evaluating operations for the correction of mitral insufficiency. It follows that the improvement may be due to the correction of stenosis rather than insufficiency in such combined procedures.

Calcification of the mitral valve was also mentioned previously as a relative contraindication. Although embolization of calcium particles from the edges of the valve at the time of mobilization remains a potential cause of morbidity and mortality, a study of the last several hundred operations reveals that this complication has been reduced by more than 75 per cent. Paradoxically some of the best results have been in such patients. When a calcified valve is encountered the surgeon must avoid loosening fragments from the valve edges and maneuver his fracture away from heavily involved areas when possible.[7] Prophylactic occlusion of the cerebral circulation has a place here.

Tricuspid stenosis is no longer a contraindication to mitral valve surgery. The chief problem is the impossibility of accurate clinical appraisal. Tricuspid stenosis has been diagnosed in our experience by the usual clinical criteria, including a gradient across the valve by catheter, but only tricuspid insufficiency was found at operation. On other occasions an apparent stenosis has been felt but not confirmed at post-mortem examination.

In order to understand this paradoxic situation several facts must be considered. First, virtually all tricuspid stenosis and insufficiency are associated with mitral disease of predominantly stenotic nature. Second, the longest commissure of the tricuspid valve is the anterior one and this may become fused without producing any hemodynamic obstruction (or tricuspid stenosis) until pulmonary hypertension causes dilatation of the right ventricle and tricuspid annulus. This in turn may tighten the minimally involved tricuspid orifice into an obstructing transverse slit. During the high flow periods of catheterization in the conscious patient this circumstance may result in a gradient across the tricuspid valve that is interpreted as evidence of anatomic stenosis. This same patient may have blood flow so reduced during anesthesia that the dilatation of the right ventricle and the tension on the tricuspid annulus are largely eliminated. The result is that the tight tambour of the tricuspid valve with its obstructing transverse slit is not found when the surgeon explores the tricuspid valve. Similarly when the mitral stenosis is relieved, pulmonary hypertension may fall and such "functional tricuspid stenosis" may disappear. This mechanism accounts for the discrepancies between clinical diagnosis, catheter measurements, and the operative findings. However, tricuspid stenosis does exist in some patients with mitral stenosis. When suspected the right auricle must be explored and the lesion corrected if present. This is possible through the same left thoracotomy incision employed for the coexisting mitral stenosis.[7]

Severe aortic disease in combination with mitral stenosis is a challenging problem rather than a contraindication to operation. The evaluation of the relative importance of these two lesions may be extremely difficult, but left heart catheterization is proving very useful here. If stenosis of both valves exists it can be corrected through the same sternum-splitting incision that has been described for the correction of pure aortic stenosis. The tricuspid valve can also be approached easily through this incision. Almost equal facility for concomitant correction of aortic stenosis is afforded by a transverse sternal extension of the conventional lateral thoracotomy for mitral valvuloplasty. In any event all procedures for the correction of aortic stenosis or regurgitation are carried out via the transaortic route approach, not the traumatic, blind, and now little-used transventricular approach.

In discussing associated aortic valvular disease it is important to emphasize that diastolic murmurs along the left sternal border must be properly interpreted. In mitral stenosis this auscultatory finding is often due to the Graham-Steele murmur of pulmonic insufficiency, and not to aortic insufficiency. Indeed a diastolic murmur along the left sternal border is very common in uncomplicated mitral stenosis. Significant aortic insufficiency generally produces left ventricular hypertrophy by x-ray or electrocardiogram, an overactive left ventricle and aorta on fluoroscopy, and an increased pulse pressure with lowered diastolic reading. This murmur, be it pulmonic or aortic in origin, is no more significant than an apical systolic murmur unassociated with other criteria of significant mitral insufficiency.

Florid rheumatic carditis remains a contraindication to operation for mitral stenosis. On the other hand, it must be appreciated that even though rheumatic activity is present, the patient with significant valvular obstruction may handle that myocardial disease better after the obstructing factor has been relieved. Many patients with mitral stenosis have recurring episodes of pulmonary infection. It is reasonable to assume that the reduction or elimination of these episodes should have a favorable influence on the rheumatic process. In general, when activity is only suspected it is disregarded. Even though so-called "signs of activity" are found in microscopic examination of the auricular biopsy, no clear correlation exists between this finding and subsequent reactivation of the rheumatic process.[8] Low-grade fever and joint pains usually are less frequent after surgery. If they occur they can be controlled with salicylates or meticorten therapy.

Other diseases, including arteriosclerotic and hypertensive cardiovascular disease, undoubtedly increase the risk. This is certainly true in the case of coronary artery disease, and has been a cause of death. However, many individuals with hypertension or arteriosclerosis of moderate degree have been operated upon for mitral stenosis and rehabilitated.

A question that naturally arises is whether the patient in Group 1, i.e., the individual with only the murmur of mitral stenosis but no symptoms, should be offered operation. This should not be done. Many such patients will live out a normal life expectancy. This is probably because valve leaflets roughened by the rheumatic process can cause murmurs in the absence of any significant

orificial narrowing. Such patients should, however, be carefully followed and re-evaluated should symptoms appear.

The foregoing considerations dictate that the physician who recognizes symptomatic mitral stenosis should consider it his obligation to seek proper evaluation of the patient for surgical relief. Only in this way can tragic deterioration of the patient be avoided. Again, the comparison to a patient with a patent ductus arteriosus can be made. The potential complications in the untreated patient, such as arterial embolization, congestive failure, pulmonary infection, and subacute bacterial endocarditis are significantly greater in mitral stenosis.

SUMMARY AND CONCLUSIONS

1. Greater diagnostic accuracy, better care before and after operation, and tenchical advances in the quality of mitral valvuloplasty for mitral stenosis have reduced the operative mortality to less than 1 per cent in patients who have not reached the stage of irreversible congestive failure.

2. Operation can be advised routinely for patients with symptomatic mitral stenosis. The risk of operation is far less than the danger of the disease.

3. Operative mortality increases twenty fold when the patient is allowed to deteriorate to the stage of refractory congestive failure. It seems little short of negligent to allow the patient to reach a late phase when relief is available at such a low risk earlier. Moreover, years later the results in these terminal patients will be less good, though their operative risk is greater. In short, the diagnosis of mitral stenosis demands consideration of operative correction just as clearly as the diagnosis of patent ductus arteriosus.

4. Further experience in the surgical management of patients with mitral stenosis tempers certain relative contraindications to operation mentioned earlier. Specifically, age over 50, auricular fibrillation, moderate mitral insufficiency, calcification of the mitral valve, associated valvular disease, and suspected rheumatic activity are no longer considered deterrants to operation. Surgery has become more urgently indicated earlier in "pure" mitral stenosis, and the era of multivalvular surgery is firmly established.

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THE BALLISTOCARDIOGRAM IN COARCTATION OF THE AORTA

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COARCTATION of the aorta is one of the well-known congenital vascular anomalies which are amenable to surgery. The exact and early diagnosis of this abnormality is life saving, and may, in most instances, be established with facility by clinical means. The use of ballistocardiography as an aid in diagnosis has been studied and a characteristic pattern observed.[1-7] While not specifically pathognomonic, such alteration in the ballistocardiogram may call the physician's attention to investigate the possibility of this disease.

The purpose of this paper is to report the ballistocardiographic findings in a well-documented series of patients with coarctation of the aorta and to show that the abnormalities recorded by the simple, direct-body ballistocardiographs are both as accurate and striking as those obtained by using more complicated table apparatus.

MATERIAL AND METHOD

Eighteen patients with coarctation of the aorta were studied. There were thirteen males and five females, ranging from 5½ to 48 years of age. In each case the diagnosis was established by accepted clinical procedures, as well as by surgery in eight cases, angiocardiography in ten, and by autopsy in one. Three patients had subaortic or aortic stenosis in addition to the aortic coarctation. One patient had the auscultatory characteristics of aortic insufficiency, probably due to relative aortic incompetence—the result of aortic dilatation or concomitant bicuspid aortic valve. Four cases showed definite evidence of left ventricular hypertrophy by electrocardiogram, vectorcardiogram, and x-ray. One of these four patients, who was in congestive failure at the time of examination, died postoperatively. Electrocardiograms and vectorcardiograms showed Wolff-Parkinson-White syndrome in two cases. However, eleven of the eighteen showed normal electrocardiograms and vectorcardiograms. Chest roentgenogram revealed characteristic notching of the ribs in nine of the eighteen cases.

The instrument used was the Pordy dual displacement and velocity apparatus[8] which is a modified direct-body Dock ballistocardiograph.[9] Both photoelectric (displacement) and electromagnetic (velocity) tracings were recorded in each case, with slight inspiration, deep inspiration, and deep expiration, under

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basal conditions. Only the qualitative appearance of the waves was studied. Postoperative ballistocardiograms were obtained in four of the eight operated cases.

RESULTS

Of the eighteen cases studied, photoelectric ballistocardiograms were abnormal in all, whereas electromagnetic tracings were abnormal in fifteen. Thus, three patients showed normal ballistocardiograms in the electromagnetic tracings.

The common abnormalities encountered were: absent I or short K waves* and a deep I wave.** One case, the oldest patient in the group, showed a tiny I in addition to a short K wave. A notched J wave with an absent K wave occurred in one case with concomitant aortic stenosis. One of the two patients showing high voltage had aortic insufficiency.

Postoperative records taken in four patients in whom surgical corrections were performed (resection and end-to-end anastomosis) showed a return of the tracings to normal. Fig. 1 refers to such a case, A. H., a 16-year-old white boy with hypertension and coarctation of the aorta. The preoperative ballistocardiographic record shows short K waves in the photoelectric, but normal patterns in the electromagnetic tracing. Six months postoperatively the photoelectric record is normal with a return of the K wave, and the electromagnetic shows a much deeper K wave. The second illustration, Fig. 2, refers to an 8-year-old girl with hypertension and coarctation of the aorta. The preoperative ballistocardiogram reveals short K waves, more noticeable in the photoelectric tracing. One year postoperatively the tracings disclose return of the K waves to normal.

DISCUSSION

A survey of the literature[1-7] indicates that the ballistocardiogram in coarctation of the aorta is almost always associated with an absent or short K wave and not infrequently with a deep I wave. It was Hamilton[3] who first mentioned that the K wave is shallow in coarctation of the aorta. Later, Brown[1] reported six cases of coarctation of the aorta in which a shortened J-K stroke was found, and of these, one returned to normal postoperatively. In 1950, Nickerson and his co-workers[2] reported seventeen cases of aortic coarctation and emphasized a common striking anomaly; the absence of the K wave. Seven of these patients in whom surgical correction of the aortic coarctation was performed showed return of the ballistocardiogram to normal, with the appearance or restoration of the K wave. Murphy[4] observed the same abnormality in eight patients with coarctation of the aorta. In three cases, after end-to-end anastomosis, the ballistocardiogram returned almost to normal. In addition, four cases had deep I waves which returned to normal postoperatively. The instrument used in the above study was the Nickerson-type apparatus. Jones and Goulder[5] found small and delayed K waves in four cases of coarctation of the aorta. Recently, Reissmann and associates,[6] using a torsion ballistocardiograph, found in all of their nine cases an I wave deep and long in duration, with a small J wave

*Photoelectric tracings of all 18 cases, electromagnetic tracings of 15 cases.

**Photoelectric tracings of 15 patients, electromagnetic tracings of 9 cases.

and an absent K wave. They noted also that in most of the cases these changes were reversed by surgery. Lyons[7] found short J-K segments in all of his cases of aortic coarctation. Similar results were obtained in this study. However, Dock[10] observed two patients with aortic coarctation in whom relatively deep K waves were present. One was a man nearly 60 years of age with congestive heart failure; another, a younger man with an aortic insufficiency. It is well-

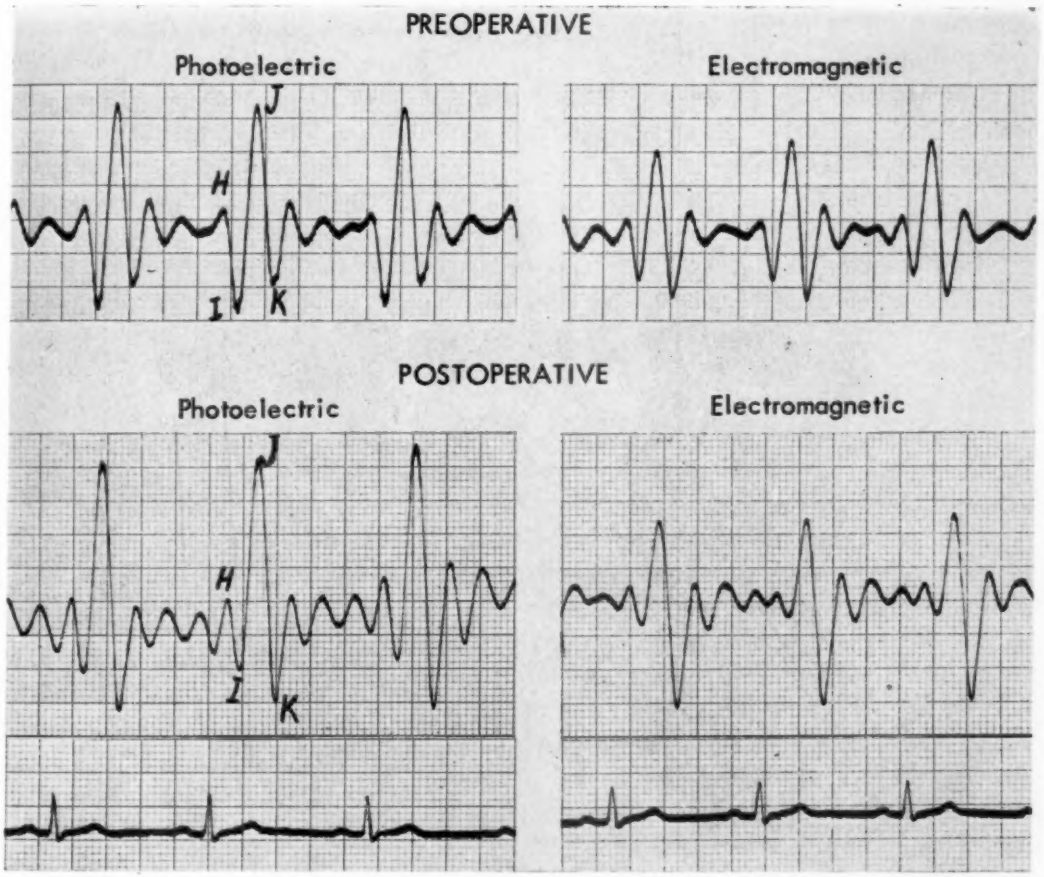

Fig. 1.—A. H., 16-year-old boy. Coarctation of the aorta, hypertension. Preoperative ballistocardiographic record: photoelectric record shows short K wave, but electromagnetic record is normal Record six months postoperatively reveals photoelectric normal with return of K wave; electromagnetic shows much deeper K wave.

known that the older patients with arteriosclerosis may show deep K waves in their ballistocardiograms, and large J-K segments have been found in patients with aortic insufficiency.[5,11,12]

Although short or absent K waves appear to be the common findings in coarctation of the aorta, there are many other conditions which may also give rise to these alterations. Elkin and Cooper,[13] in 1949, recorded the ballistocardiograms of nine patients with insidious thrombosis of the aorta (the Leriche syndrome). With the use of the Nickerson-type apparatus, they observed the K wave to be shallow with a high cut-off. This same abnormality of the K

wave was also found by Murphy[4] in ten patients with thrombosis of the aorta. Postoperative records obtained from two of these cases showed a return of the K wave to normal size. Similar K-wave abnormality in the above syndrome was observed by others.[10,14]

Dock and associates[10] noted that obese women, especially those wearing tight corsets, exhibit short K waves. Some small, normotensive subjects may also present such findings. These changes are seen occasionally in persons standing quietly for some time before the ballistocardiogram is taken. Jones and Goulder[5] found that the K wave is small in normal subjects with vertical hearts, whereas the K wave is deep when the heart is horizontal. Shock[9,15] may also produce the same abnormality. A short K wave has also been observed with congenital heart diseases. Bixby[16] noted, in a pregnant woman with patent ductus arteriosus, a short K wave which returned to normal postoperatively. This abnormality was present in one of our ten cases with patent ductus arteriosus.[17] Other congenital heart diseases, such as interatrial septal defect, Eisenmenger's complex and interventricular septal defect may also show short K waves.[17] K-wave shortening may occur in acquired heart disease, and we have reported one case of left bundle branch block with arteriosclerotic heart disease and a short K wave.[8]

Normally, the K wave is slightly deeper than the I wave, so it is usually the deepest negative wave of the ballistocardiogram. It reflects the deceleration of blood in the aorta and its impact with small peripheral vessels.[3] This deceleration of the blood in the descending aorta and the flow against peripheral resistance both produce a force which moves the body in a footward direction, recording the K wave of the ballistocardiogram. In patients with coarctation of the aorta or chronic occlusion of the abdominal aorta, the interruption of the blood flow in the aorta by the stenotic area reduces footward blood flow,[1,2,4] and deceleration of the blood occurs much earlier than normally since it meets resistance earlier. This blocks[11] footward forces which are usually responsible for the production of the K wave. A portion of the blood, going through small collateral channels[6] proximal to the obstruction may also produce more deceleration or, perhaps, some forces of different direction which may oppose those producing the K wave. In addition, it is quite possible that, during the development of the K wave, sudden resistance to the blood flow from the obstruction may produce a headward recoil of the ballistic system opposing the footward forces during deceleration of the blood in the descending aorta. This abnormal force may also obliterate the occurrence of the normal K wave, causing a short or absent K wave. Nickerson,[15] by constructing a simple model of the heart and aorta, showed that shortening or constriction of the descending aorta resulted in a diminished or absent K wave.

Very recently, Deuchar and his co-workers,[18] using an aperiodic ballistocardiograph,[19] attempted to support Starr's early idea that the K wave may be an artefact arising from after-oscillation of an undamped system.[20] They assumed that the K wave represented a part of "passive after-vibrations" since they could not observe forces corresponding to the K wave. However, normal tracings taken with different periodic ballistocardiographs of different physical

properties invariably show the presence of K waves. Second, short K waves are seen in pathologic conditions such as coarctation of the aorta and the Leriche syndrome. Third, the deep K wave of hypertension returns to normal after correction of the pathologic state.[1,2,4,6,21] Therefore, it is difficult to believe

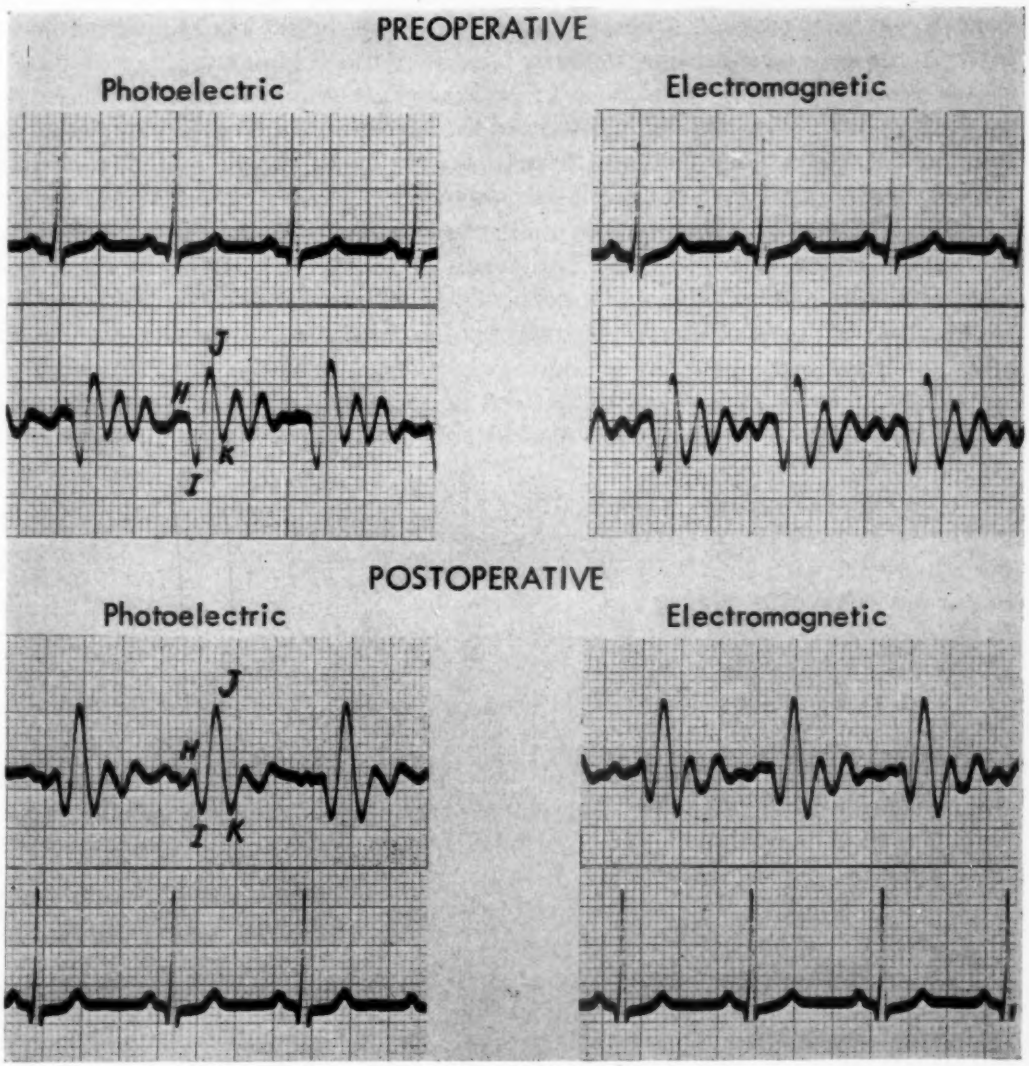

Fig. 2.—B. S., 8-year-old girl. Coarctation of the aorta; hypertension. Ballistocardiogram: preoperative photoelectric record shows very short K wave but electromagnetic shows slightly short K wave. Record one year postoperatively reveals return of K wave with normal photoelectric and electromagnetic records.

the explanation of the K wave as merely an artefact. Using the findings of Deuchar and associates[18] with the aperiodic tracings, the short K wave of periodic systems in aortic coarctation appears to be due to an abnormal headward force occurring at the time of the K.

The K wave is influenced by many factors. Peripheral resistance plays an important role in the amplitude of this wave. Decreased peripheral resistance

shortens it.[15] The reverse is also true, i.e., increased peripheral resistance increases the amplitude of the K wave in hypertension and arteriosclerosis.[10,21-25] In hypotension the K wave is shallow.[22] Low cardiac output and the consequent decrease in flow in the aorta and its branches diminishes the amplitude.[9,15] It is conceivable that the same mechanism holds true for the explanation of the short K wave in congenital heart disease with left-to-right shunt. In patients with patent ductus arteriosus, blood passing into the pulmonary artery through the ductus reduces the blood flow going down into the aorta.[26] In the other congenital heart diseases with intracardiac left-to-right shunt, it is probable that the decreased blood flow in the aorta, due to the diminished left ventricular output, may be the cause of the short K wave.[17]

The influence of different types of instruments on the K wave is more obvious than its effect on other waves. The depth of the K wave depends upon the type of ballistocardiograph used. In normal subjects the K wave is usually slightly deeper than or equal to the I wave on records taken with a high-frequency and undamped apparatus.[27-29] The low-frequency, critically damped table of Nickerson gives an almost similar pattern in normal individuals.[29,30] Dock and associates[10] state that the K wave may be shorter than the I wave in many normal subjects. However, in a study of 319 healthy young soldiers, using a Dock portable electromagnetic ballistocardiograph, Abrams[31] found the K wave to be the most prominent and deepest negative component. This has also been our experience with the electromagnetic tracings of the dual ballistocardiograph in normal subjects. The K wave is, normally, slightly deeper than the I wave in photoelectric tracings, but in the electromagnetic tracings it is much deeper.[8] In normal tracings taken with the Nickerson apparatus the K wave is usually similar to those taken with the high-frequency table. However, in the presence of pathologic conditions with short K waves the Nickerson table exaggerates these abnormalities and shows them more obviously.[15] This is due to the fact that low-frequency components are better recorded with this instrument[26] than with the high frequency table. Since all of the various ballistocardiographs have different physical properties, it is not surprising to observe differences in the tracings of each. In the presence of pathologic conditions, these differences in wave patterns become more pronounced.

In our eighteen cases with coarctation of the aorta, a short or absent K wave was invariably present in all photoelectric (displacement) tracings, whereas the same abnormality was shown in only fifteen electromagnetic (velocity) tracings. The abnormality of the K wave was very obvious in photoelectric tracings, as is seen in those taken with the Nickerson apparatus. These findings confirm the previous observations of Frankel and associates[11] and Pordy and associates[33] that the "photoelectric cell pick-up" is more suitable for detecting the "high take-off" of the K wave in aortic coarctation. Thus, in this condition, photoelectric (displacement) type ballistocardiographs are believed to yield more dependable results.[25,32]

Murphy[4] noted that four of his eight cases of coarctation of the aorta showed a deep I wave in addition to a short K wave. This abnormality returned to normal after surgery. Reissmann and associates[6] made the same observations.

A deep I wave was present in fifteen out of eighteen (photoelectric) and nine out of eighteen (electromagnetic) tracings in our study and returned to normal in four cases after surgical correction. This wave abnormality, as in the K wave alterations, was more striking in the photoelectric tracings.

Normal downward or negative I waves are believed to be due to caudal displacement of the body caused by recoil from the ejection of blood into the aorta and the pulmonary artery in early systole.[3,15,20] The explanation of the deep I wave seen in coarctation of the aorta is not clear. Reissmann[6] explained it by the headward shift of the center of gravity.

As short or absent K waves are seldom seen in hypertension without congestive heart failure, in the exclusion of the aforementioned condition, short K waves in hypertensives suggest coarctation of the aorta. There is a constant correlation between coarctation of the aorta and short or absent K waves, as well as a high degree of correlation with deep I waves. The ballistocardiogram, therefore, is a useful diagnostic tool among the other measures for the diagnosis of coarctation of the aorta, especially in doubtful cases.

SUMMARY

1. Eighteen cases of coarctation of the aorta have been studied. All showed absent or short K waves in the photoelectric tracings. I waves were also deep in fifteen patients. Electromagnetic tracings were found to be normal in three of the eighteen cases.

2. Photoelectric (displacement) apparatus displays the abnormalities of coarctation of the aorta more obviously and strikingly than the electromagnetic (velocity) apparatus.

3. Absent or short K waves seem to be a constant ballistocardiographic finding in coarctation of the aorta when photoelectric tracings are recorded.

4. In the presence of hypertension, the above-mentioned ballistocardiographic findings are suggestive of aortic coarctation.

5. No correlation was seen between the degree of hypertension in the upper extremities and the degree of the ballistocardiographic abnormalities.

6. The results of this study indicate that the simple direct-body ballistocardiographs show abnormalities in coarctation of the aorta as clearly as those obtained by the other complicated table-model apparatus.

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COMPARATIVE VASOCONSTRICTOR EFFECTS OF INHALING TOBACCO SMOKE IN WARM AND COOL ENVIRONMENTS AND BEFORE AND AFTER ABSTINENCE FROM TOBACCO

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IT IS generally agreed that the inhalation of tobacco smoke causes vasoconstriction in the foot.[1] However, quantitative data concerning the relative intensity of this vasoconstriction are not available. The experiments described herein were designed to compare foot blood flow responses to smoking under different control conditions of vasomotor activity, to compare the vasoconstrictor response to smoking with that produced by a cool environment and to determine whether or not a period of abstinence from tobacco results in a more profound vasoconstrictor response to smoking.

METHOD

General.—The subjects were normal male house officers whose ages ranged from 26 to 33 years. All of them habitually inhaled tobacco smoke and regularly consumed more than one pack of cigarettes per day. The studies were carried out in a constant temperature room. Plethysmographic measurements of foot blood flow were made under conditions of mild vasodilatation produced by exposure of the subjects to a room temperature of 83° F. (warm room) and were repeated later in each subject under conditions of mild vasoconstriction produced by exposure to a room temperature of 68° F. (cool room). Observations were made during the subject's regular smoking habit and repeated after 24 to 48 hours of abstinence from tobacco. All tests were conducted 2½ to 3 hours after the noon meal. When tests were done during the regular smoking habit, each subject finished his last cigarette at the time he reported to the laboratory. Subjects were studied lying nude except for shorts in the supine position with the posterior aspect of the leg and foot at heart level. The subjects were encouraged to relax but were not permitted to sleep. They were asked not to talk except to report unusual sensations.

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Plethysmographic Technique.—The foot and ankle to a point just proximal to the malleoli was enclosed in a Wahmann Foot Plethysmograph.* A loose-fitting thin rubber stocking was constructed to enclose the foot. The open end of this stocking was everted and permanently attached to the flange at the open end of the plethysmograph. The space between the ankle and the orifice of the plethysmograph was closed by snug ankle-contoured masonite plates which were held firmly against the flange by brass plates. This technique for enclosing the part is similar to that previously described.[2,3] Water pressure in the plethysmograph forced the rubber stocking into loose folds against the skin and the inner sides of the masonite plates and no air was trapped between any of these surfaces.

The water level within the plethysmograph was such that the hydrostatic pressure was equal to or very slightly greater than natural local venous pressure. Under this condition the effective venous pressure (internal venous minus external water pressure) was reduced to a low constant value.[2] Thus at the beginning of each blood flow measurement, the vein walls could distend freely when venous congestion was produced by inflating a 10 cm. wide pneumatic cuff around the ankle proximal to the plethysmograph. The rates of change of foot volume were recorded by means of a sensitive Brodie bellows. In each experiment the minimum venous occlusion pressure required to produce the maximum rate of increase in foot volume was used. This pressure was usually about 30 mm. Hg.[4]

Testing Procedure.—The plethysmograph was applied to the left foot and a copper constantan thermocouple to the tip of the right great toe. Water temperature in the plethysmograph was maintained at 89° F. in both warm and cool room studies. Room temperature was controlled within ± 1° F. Foot blood flow measurements were made at the rate of three for each five-minute period. Toe temperature and room temperature were monitored continuously. Sphygmomanometric blood pressure determinations and radial pulse rates were recorded at five-minute intervals.

After a minimum of one hour of exposure to the constant room temperature and after foot blood flow had become reasonably stable, the subject was asked to smoke two cigarettes of his regular brand. Inhalation of the smoke was at the rate and depth customary for each subject. No low nicotine, "king" size, or filter tip cigarettes were used. All observations were continued for 30 to 60 minutes after the beginning of smoking.

In the illustrations foot blood flow is reported in cubic centimeters per minute per 100 c.c. of foot tissue. Foot blood flow responses to smoking are expressed as per cent reductions from control blood flow values. All responses are calculated from the average of all control blood flow measurements and the average of the 18 individual blood flow determinations obtained during the 30 minutes following the beginning of smoking.

*George H. Wahmann Manufacturing Company, Baltimore, Md.

RESULTS AND DISCUSSION

General Observations.—The time required to smoke the two cigarettes varied among the different subjects as did the rate of inhalation. The smoking periods lasted 10 to 18 minutes and the inhalation rates ranged from 1 to 3 per minute. Fig. 1 shows data obtained from one subject. Increases in pulse rate and blood pressure and decreases in skin temperature were observed in each experiment.

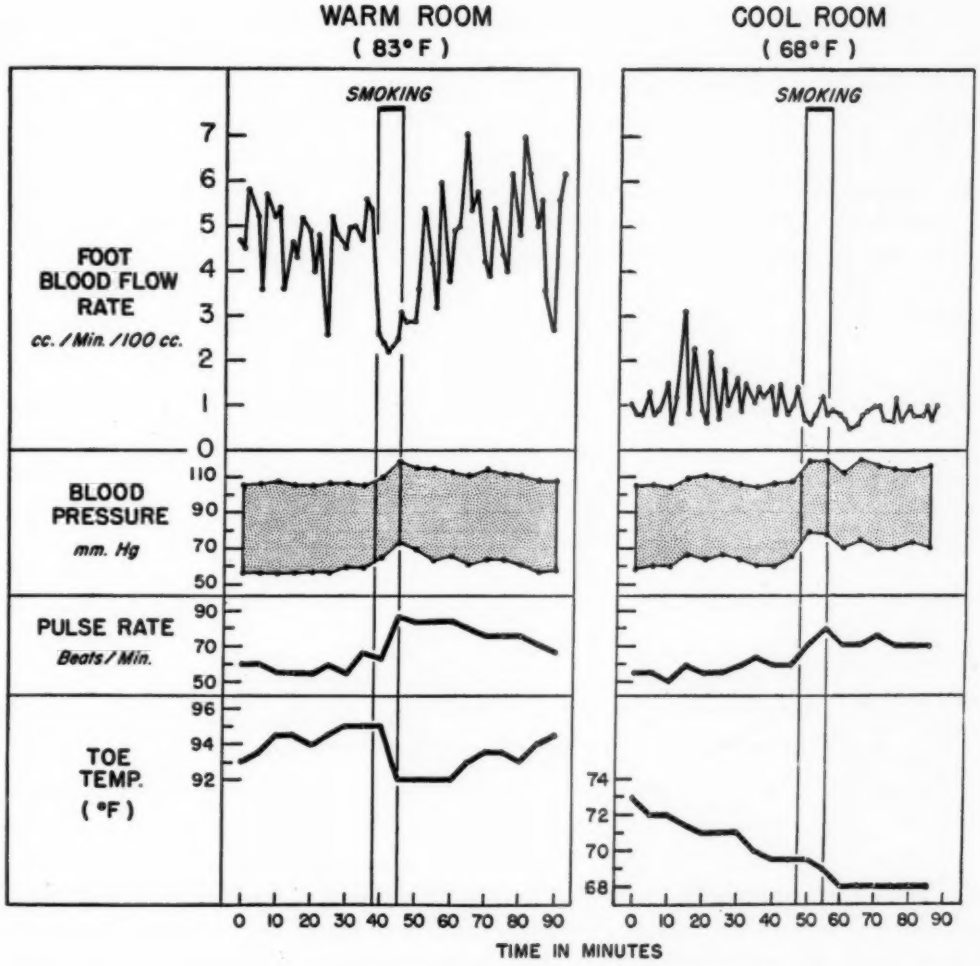

Fig. 1.—Data obtained from two experiments (Subject J.C.).

These changes were similar in magnitude to those reported by others.[5] While there were the usual normal spontaneous fluctuations in foot blood flow, a decrease in the average flow occurred on smoking under all conditions of the study except in 3 of 31 experiments (Table I). In these three experiments there was no change in average blood flow from the control. However, in these three cases smoking was associated with increases in blood pressure and pulse rate and reductions in the variations of blood flow.

TABLE I. FOOT BLOOD FLOW RESPONSES TO SMOKING TWO CIGARETTES AT ROOM TEMPERATURES 83° F. AND 68° F.

SUBJECT	WARM ROOM			COOL ROOM			VARIATION OF COOL FROM WARM ROOM SMOKING RESPONSES
	CONTROL (C.C./MIN./100 C.C.)	WITH SMOKING (C.C./MIN./100 C.C.)	RESPONSE TO SMOKING (PER CENT DECREASE)	CONTROL (C.C./MIN./100 C.C.)	WITH SMOKING (C.C./MIN./100 C.C.)	RESPONSE TO SMOKING (PER CENT DECREASE)	(PER CENT UNITS)
L.P.	—	—	—	1.5	1.3	13	—
	4.5	2.5	44	1.8	1.0	44	0
	3.6	2.6	28	1.8	1.2	33	+ 5
J.C.	5.9	5.3	10	1.0	0.7	30	+20
	4.7	4.1	13	1.2	0.8	33	+20
	5.8	3.5	40	—	—	—	—
R.C.	8.4	6.3	25	1.8	1.0	44	+19
	10.2	9.3	9	1.2	1.0	17	+ 8
	6.5	5.1	21	0.9	0.8	11	−10
J.B.	2.2	2.2	0	2.1	1.5	29	+29
	2.4	2.4	0	0.9	0.8	11	+11
R.R.	3.0	2.4	20	1.0	1.0	0	−20
	3.1	2.5	19	—	—	—	—
	4.8	3.8	21	1.4	1.3	7	−14
S.S.	8.7	7.0	19	1.5	1.4	7	−12
	9.2	4.1	55	2.0	1.5	25	−30
	7.6	4.3	43	—	—	—	—
L.K.	7.2	5.5	24	—	—	—	—
Total Group Average	5.75	4.28	23.0	1.44	1.09	21.7	—
Paired Group Average	5.70	4.39	20.4	1.43	1.08	22.4	+2.0

The vasoconstrictor response in the foot usually began with the first inhalations of smoke but, in many cases, tended to remit even during the smoking period. In the warm room vasoconstriction usually persisted for 20 to 40 minutes. This effect tended to be prolonged to 20 to 50 minutes in the cool room. Changes in toe temperature consistently lagged behind changes in blood flow.

Smoking in the Warm and Cool Rooms.—In 17 warm room experiments (Table I) the absolute reductions in foot blood flow in response to smoking two cigarettes ranged from zero to 5.1 c.c./min./100 c.c. of foot tissue and averaged 1.5 c.c./min./100 c.c. In 14 cool room experiments these reductions ranged from zero to 0.8 c.c./min./100 c.c. of foot tissue and averaged 0.3 c.c./min./100 c.c. Despite this marked absolute difference, the range of the responses in the warm and in the cool rooms expressed as per cent reductions from control values were

remarkably similar (Fig. 2,*A*). Thus, in 13 paired experiments (Table I) warm room reductions in foot blood flow with smoking averaged 20.4 per cent and the cool room reductions averaged 22.4 per cent. In these 13 tests the distribution of variations of cool room from warm room smoking responses was almost symmetrical (Fig. 3,*A*).

Smoking after Abstinence From Tobacco.—In 11 paired experiments (Table II) the smoking test was performed before and after 24 or 48 hours of abstinence from tobacco. The ranges of the smoking responses observed before and after tobacco abstinence (Fig. 2,*B*) were very similar as were the group averages. Before tobacco abstinence, foot blood flow reductions with smoking ranged from 0 to 44 per cent and averaged 18.4 per cent below the control levels. After tobacco abstinence these responses ranged from 0 to 55 per cent and averaged 20.6 per cent. The distribution of variations of responses observed after 24 or 48 hours of tobacco abstinence from those observed before abstinence was almost symmetrical (Fig. 3,*B*). In five experiments there was a greater reduction in foot blood flow when smoking after tobacco abstinence; in five there was a smaller reduction in flow, and in one there was no change. Most of the subjects spontaneously reported mild symptoms of giddiness or light-headedness

TABLE II. FOOT BLOOD FLOW RESPONSES TO SMOKING TWO CIGARETTES BEFORE AND AFTER 24 OR 48 HOURS OF ABSTINENCE FROM TOBACCO

SUBJECT	BEFORE ABSTINENCE FROM TOBACCO			AFTER ABSTINENCE FROM TOBACCO			VARIATION OF POST-TOBACCO ABSTINENCE FROM PRE-TOBACCO ABSTINENCE SMOKING RESPONSES (PER CENT UNITS)
	CONTROL (C.C./MIN./100 C.C.)	WITH SMOKING (C.C./MIN./100 C.C.)	RESPONSE TO SMOKING (PER CENT DECREASE)	CONTROL (C.C./MIN./100 C.C.)	WITH SMOKING (C.C./MIN./100 C.C.)	RESPONSE TO SMOKING (PER CENT DECREASE)	
L.P.	1.5	1.3	13	1.8	1.0	44	+31
J.C.	5.9	5.3	10	4.7	4.1	13	+ 3
	1.0	0.7	30	1.2	0.8	33	+ 3
R.C.	6.5	5.1	21	10.2	9.3	9	−12
	1.8	1.0	44	1.2	1.0	17	−27
J.B.	2.2	2.2	0	2.4	2.4	0	0
	2.1	1.5	29	0.9	0.8	11	−18
R.R.	4.8	3.8	21	3.0	2.4	20	− 1
	1.4	1.3	7	1.0	1.0	0	− 7
S.S.	8.7	7.0	19	9.2	4.1	55	+36
	1.5	1.4	7	2.0	1.5	25	+18
Average	3.40	2.78	18.4	3.42	2.58	20.6	+2.4

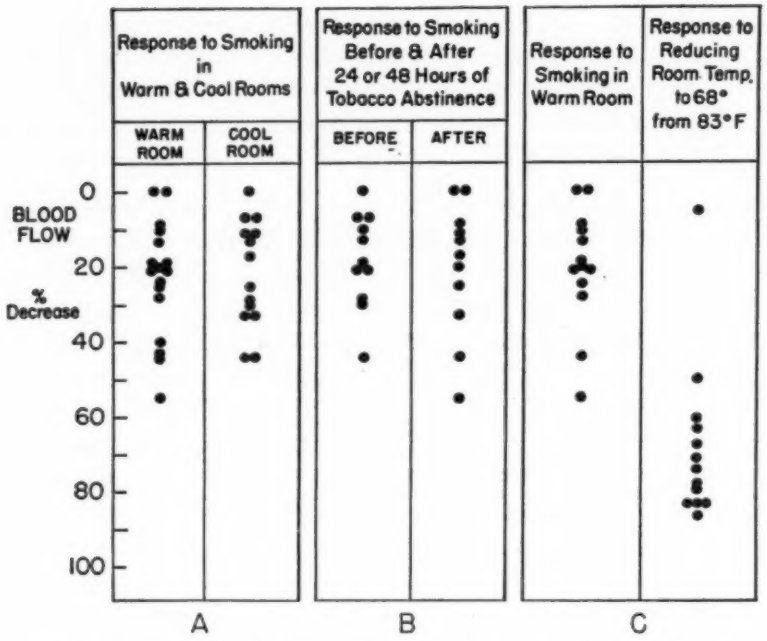

Fig. 2.—Foot blood flow response to smoking is plotted as per cent decrease from the control level. Smoking responses in the warm and cool rooms and after tobacco abstinence fell into the same general range. Foot blood flow decreases with reducing room temperature were greater than those associated with smoking under any conditions of the study.

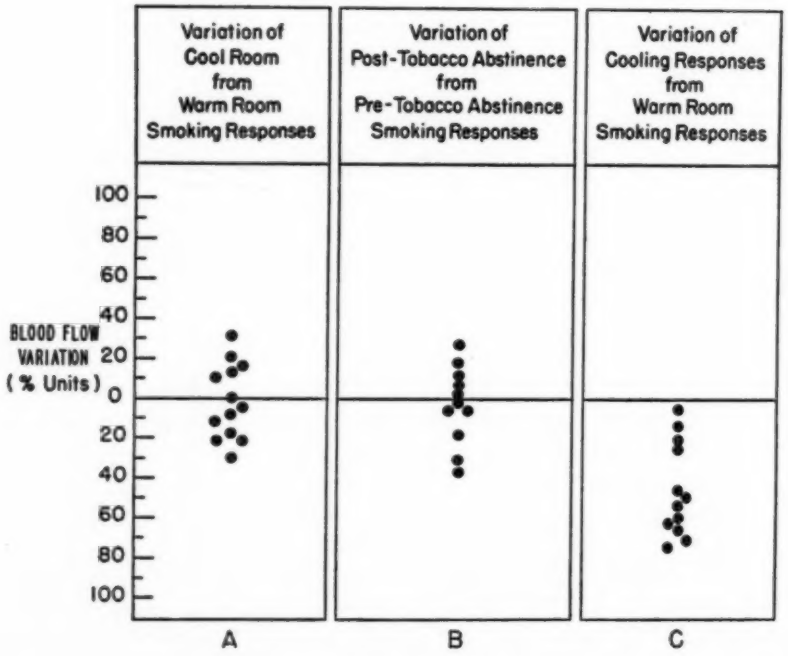

Fig. 3.—The line at zero in each frame represents smoking responses observed during initial testing conditions. Values below the line represent greater responses (larger reductions in foot blood flow) and values above the line represent smaller responses when foot blood flow measurements were repeated under the different conditions.

when smoking after abstinence from tobacco. These symptoms were not associated with any accentuation of the vasoconstrictor response in the foot or with any unusual change in blood pressure or pulse rate.

Under the conditions of these experiments abstinence from tobacco did not alter the vasoconstrictor response to smoking.

Foot Blood Flow Changes With Reduction of Room Temperature.—In 13 paired experiments, the foot blood flow response to a reduction in room temperature to 68° F. from 83° F. was compared to the foot blood flow response to smoking in the warm room (Table III). In all cases a greater reduction in foot blood flow occurred on cooling the room than on smoking two cigarettes (Fig. 3,*C*). The reductions in flow with smoking ranged from 0 to 55 per cent and averaged 20.4 per cent. Flow reductions with cooling ranged from 5 to 86 per cent and averaged 67.8 per cent. With but two exceptions (Fig. 2,*C*) all the cooling responses were greater than the greatest smoking response.

TABLE III. FOOT BLOOD FLOW RESPONSES TO SMOKING TWO CIGARETTES IN THE WARM ROOM AND TO REDUCING ROOM TEMPERATURE TO 68° F. FROM 83° F.

SUBJECT	CONTROL IN WARM ROOM (C.C./ MIN./ 100 C.C.)	WITH SMOKING (C.C./ MIN./ 100 C.C.)	WITH COOLING (C.C./ MIN./ 100 C.C.)	RESPONSE TO SMOKING (PER CENT DECREASE)	RESPONSE TO COOLING (PER CENT DECREASE)	VARIATION OF COOLING FROM WARM ROOM SMOKING RESPONSES (PER CENT UNITS)
L.P.	4.5	2.5	1.8	44	60	+14
	3.6	2.6	1.8	28	50	+22
J.C.	5.9	5.3	1.0	10	83	+73
	4.7	4.1	1.2	13	74	+61
R.C.	8.4	6.3	1.8	25	79	+54
	10.2	9.3	1.2	9	83	+74
	6.5	5.1	0.9	21	86	+65
J.B.	2.2	2.2	2.1	0	5	+ 5
	2.4	2.4	0.9	0	63	+63
R.R.	3.0	2.4	1.0	20	67	+47
	4.8	3.8	1.4	21	71	+50
S.S.	8.7	7.0	1.5	19	83	+64
	9.2	4.1	2.0	55	78	+23
Average	5.70	4.39	1.43	20.4	67.8	+47.3

SUMMARY AND CONCLUSIONS

Under all conditions of the study, smoking two cigarettes resulted in reductions in foot blood flow in 28 of 31 experiments. These reductions ranged from 9 per cent to 55 per cent and averaged 22.3 per cent. Smoking in the warm room, the cool room, and after 24 or 48 hours of abstinence from tobacco caused decreases in foot blood flow which fell into the same general range. Under these three conditions the average reductions in flow were, respectively, 23.0 per

cent, 21.7 per cent, and 20.6 per cent. This striking similarity of response suggests that these different control levels of vasomotor activity do not alter significantly the vasoconstrictor effects of smoking cigarettes. Under the conditions of this study smoking was a less intense vasoconstrictor stimulus than cooling the environment from 83° F. to 68° F.

We wish to acknowledge the valuable technical assistance of Miss Barbara A. Sears.

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Clinical Reports

ALLERGIC SHOCK IN HUMANS: REPORT OF TWO CASES WITH ELECTROCARDIOGRAPHIC FINDINGS

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NEW YORK, N. Y.

IT IS the purpose of this paper to describe and discuss the clinical and electrocardiographic findings in anaphylactoid reactions following the administration of histamine and acetylsalicylic acid. While such allergic responses have been observed before,[1,2] analysis of the associated changes in the 12-lead electrocardiogram during the shock state, and their possible relationship to the mechanism of anaphylaxis have not been reported.

CASE REPORTS

CASE 1.—A. H., a 51-year-old white man, was admitted to The Mount Sinai Hospital on July 22, 1955, for elective gastrectomy. He complained of duodenal ulcer pain for a number of years. His symptoms had not responded to conventional therapy in the six months prior to admission. The ulcer had been repeatedly visualized roentgenographically. For a number of years preceding admission he had been examined at regular intervals by his family physician who found no impairment of cardiac function or decrease in myocardial reserve. There was no history of angina. The patient had suffered from "asthma" between the ages of 11 and 17, but had had no symptoms for the past thirty-four years. As part of the preoperative procedure, a Rehfuss test with histamine was performed on the morning of July 25. Histamine phosphate injection, 0.5 mg., was given by a graduate nurse. A small intramuscular needle, No. 22 gauge, was used. The drug was administered deep subcutaneously in the buttock. The nurse reported that the barrel of the syringe was withdrawn. No blood entered the syringe at any time prior to the injection. Within four or five seconds after the histamine had been given the patient complained of inability to breathe. He gasped for air. Two or three seconds later he was unresponsive, perspiring profusely, breathing stertorously, and in apparent severe clinical shock. His radial pulse was unobtainable. Within two minutes a resident physician administered 1 c.c. of 1:1000 epinephrine in aqueous solution subcutaneously and 50 mg. of Benadryl intravenously. The shock state persisted for five minutes and was followed by gradual recovery. The arterial pressure, previously unobtainable, rose to 90/40 mm. Hg. At the same time, the radial pulse became palpable. The

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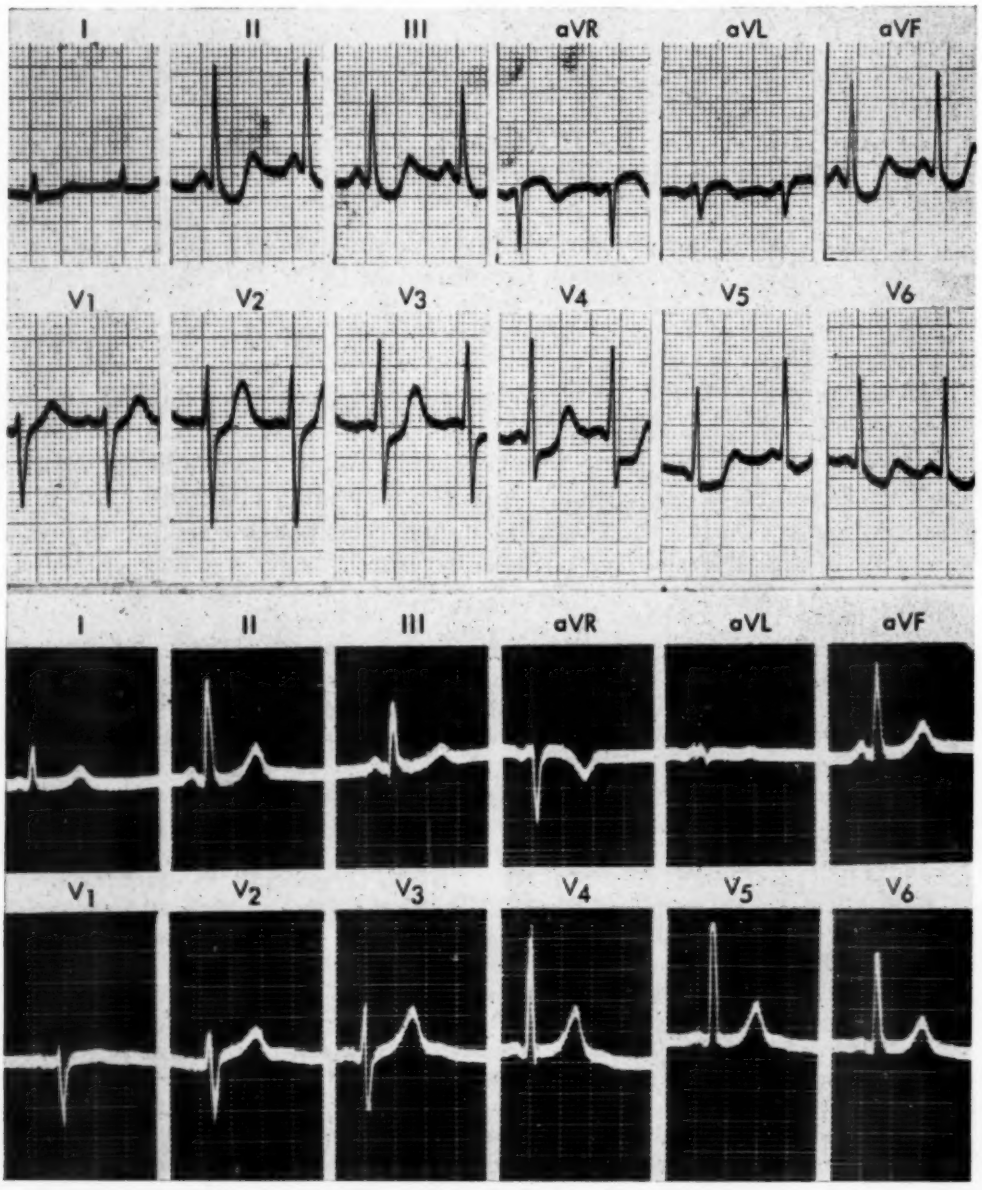
profuse diaphoresis diminished. During the next ten minutes the patient complained of severe precordial pain, typically anginal in nature, which he described as, "as if someone were tightening a chain 'round my chest." This sense of constriction persisted for fifteen minutes, during which time an electrocardiogram was taken (Fig. 1,*A*). This revealed RS-T segment depression in the standard and precordial leads and significant generalized T-wave changes. There was marked

A.



B.

Fig. 1.—*A*, July 25, 1955. Marked RS-T segment depression in Leads II, III, aV_F, and V_2 to V_6, with elevation in aV_R, aV_L. Diphasic T waves in standard limb leads and V_5 to V_6. No Q waves present. *B*, July 26, 1955. Tracing taken the following day. RS-T segments have all returned to isoelectric level. T waves are now upright.

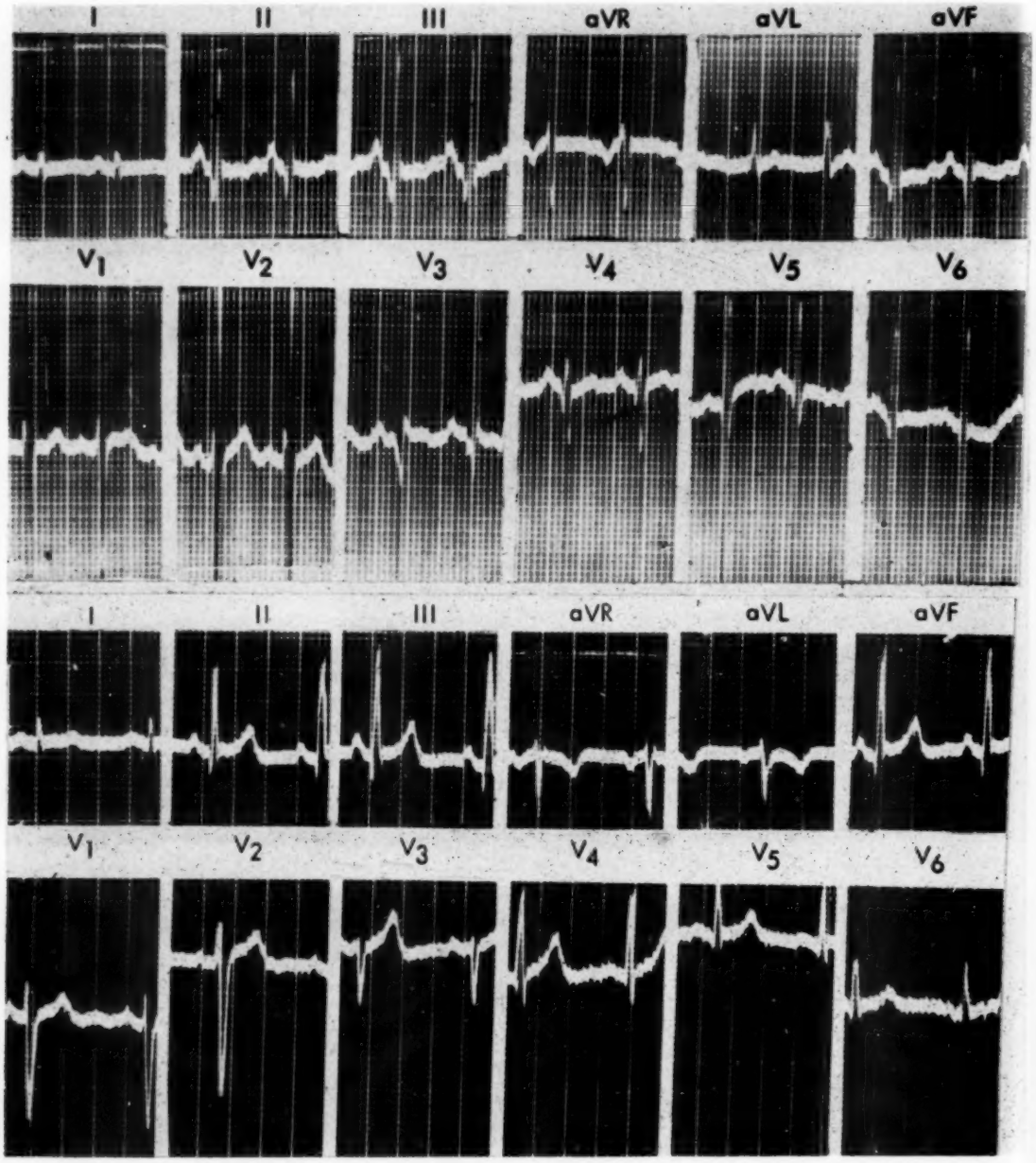
nausea and vomiting. The expiratory phase of respiration was prolonged. By evening the patient was free from complaints. An electrocardiogram taken the next day was normal (Fig. 1,*B*). Forty-eight hours after this acute period a subtotal gastrectomy was performed, and was followed by an uneventful recovery. The patient was discharged on the fourteenth hospital day. On October 18, he returned to the Out-patient Department for re-evaluation of his cardiac status. The electrocardiogram remained normal and a Master double two-step test was negative. Clinically he has remained asymptomatic since his discharge.

CASE 2.—J. R., a 31-year-old white man, was admitted to this hospital from the Emergency Room on the evening of May 1, 1952, in a state of clinical shock. He had ingested 2 aspirin tablets a short time before. This patient had been well until 1943 at which time he developed asthma while serving in the armed forces. In the intervening years his asthmatic condition had become progressively more severe, necessitating frequent hospitalization and intensive therapy. In 1951, following a tooth extraction, he was given aspirin for pain. This precipitated a very severe "asthmatic attack." He avoided the use of this drug after this episode. During the week prior to admission there was an exacerbation of his asthmatic state. He came daily to the Emergency Room for relief of respiratory symptoms. Two days prior to admission he developed pleuritic pain in the left axillary area. He was seen and examined in the Out-patient Department the afternoon of admission and was given aspirin tablets. Shortly after returning home he took two of these tablets. Within twenty minutes he began vomiting, became dyspneic, started to wheeze, and soon lapsed into a state of unconsciousness. When brought to the Emergency Room a short time later, he was in a state of clinical shock. Radial pulse and arterial pressure were not obtainable. There was a marked cyanosis. Respiration consisted of occasional gasps. Artificial resuscitation was begun immediately. In addition, he was given oxygen and 2 c.c. of Coramine, 60 mg. of caffeine sodium benzoate, and 0.5 Gm. aminophylline intravenously, and 0.3 c.c. of 1:1000 aqueous solution of epinephrine subcutaneously. Within a few minutes his condition improved. Respirations became regular. The pulse rate was 152 per minute and the arterial pressure 110/70 mm. Hg. Physical examination immediately after the acute episode revealed an increase in the anteroposterior diameter of the chest, loud musical wheezes in both phases of respiration, and prolongation of expiration. The apical impulse was in the fifth intercostal space in the midclavicular line. Heart sounds were barely audible. The second pulmonic sound was accentuated, but no murmurs were heard. There was no clubbing. A chest film revealed an area of diffuse infiltration near the cardiac apex in the left lower lobe. The heart was normal in size and configuration. An electrocardiogram was taken shortly after initial response to therapy (Fig. 2,*A*). This revealed abnormally tall P waves in Leads II, III, and aV_F and a deep, wide, notched Q wave in V_3. The patient was then admitted to the ward where he remained for seven weeks. He was treated with ACTH which was gradually tapered off and finally discontinued. Follow-up electrocardiograms were taken in order to evaluate the presence, if any, of permanent cardiac damage (Figs. 2,*B* and 3). The abnormal Q wave previously seen in V_3 was no longer present and the P waves had diminished in size. He was discharged on June 24, 1952.

DISCUSSION

In man, the symptoms of allergic shock are anxiety, cough, cyanosis, dyspnea, peripheral circulatory collapse, coma, and death. When this reaction is early and explosive, as in the cases presented above, it is designated "anaphylactoid." There is general agreement that whatever the ultimate mediating agent may be, this severe state results from a specific antigen-antibody reaction. Much experimental work has been done to isolate the actual shock-producing material which is instantaneously released from the so-called "shock organs" as a product of this interaction. Many investigators believe that histamine or a histamine-like substance is responsible,[4,11] while others have failed to demonstrate its presence in increased amounts in many allergic situations.[12] Where histamine in excessive amounts is not demonstrable, then some other agent or toxin is implicated.[13]

A.



B.

Fig. 2.—*A*, May 1, 1952. Sinus tachycardia. Note tall, notched P waves in standard limb leads. Deep QS present in V_3. Significant Q waves in V_4. With normal Q in V_5 and V_6. RS-T segments are isoelectric. Note lowered T waves in all leads. *B*, May 6, 1952. Tracing taken five days later. P waves have become smaller. Small R wave now present in V_3 and Q wave in V_4 is smaller. T waves are now upright.

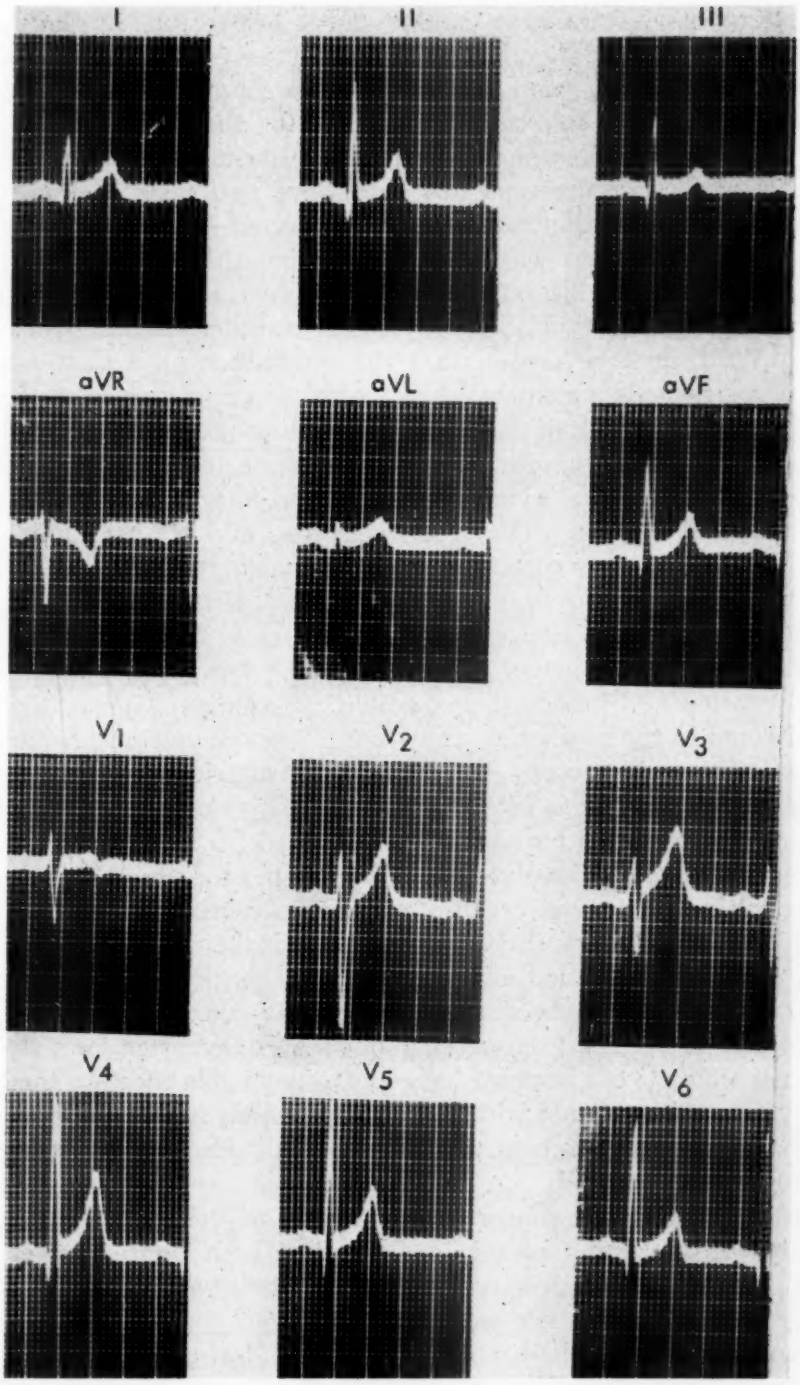


Fig. 3.—Tracing taken ten days after Fig. 2,*A*. P waves now normal. R taller in V_3. T waves normal.

Whether or not histamine is the sole agent responsible for the signs and symptoms of every type of allergic shock, there can be no doubt that it accounts at least for some. It is beyond the scope of this communication to determine the nature of the actual substance responsible for the mechanism of allergic shock, particularly since there is no common agreement on this question among allergists. However, we are reporting the above two cases of frank allergic shock because of the cardiovascular effects reflected electrocardiographically. In the first case, where there was a history of asthma, the entire clinical picture was obviously due to the histamine which had been injected.[14] In the second patient, too, there was a typical anaphylactoid reaction following the ingestion of aspirin. We cannot be certain that the ultimate clinical picture was due to release of endogenous histamine, although this is strongly suspected.

In addition to the lack of agreement concerning the nature of the effecting substance, the actual mechanism of the shock state itself has not been completely clarified. Signs and symptoms appear to vary somewhat among different animals and in man. They are widespread and are not limited to any one organ system. In any case of allergic shock, the total clinical picture apparently depends on the site of release and action of the mediating agent.

The shock state associated with an anaphylactoid reaction has three components; peripheral, pulmonary, and cardiac. The peripheral factors are the result of dilatation and increased permeability of the capillaries. This results in stasis of blood in the capillaries, anhydremia, poor venous return, and consequent decreased cardiac output.[15] The small prearterioles also dilate, contributing to a further decrease in blood pressure.[16] This capillary and prearteriolar dilatation can be produced by histamine.

The specific mode of involvement of the respiratory mechanism varies in different animals. The shock organ of the guinea pig is the smooth muscle of the bronchi and bronchioles, while in the rabbit it is the media of the pulmonary arterioles. The manifestation of anaphylactoid shock in the guinea pig is therefore chiefly asphyxia, because of bronchiolar constriction; in the rabbit right heart failure results from sudden pulmonary hypertension. In normal persons small amounts of histamine have only a negligible effect on the bronchovascular system. In patients with respiratory disease such as asthmatic bronchitis or bronchial asthma, however, similar small doses of histamine have a bronchoconstrictor effect.[11,17]

There is no agreement concerning the nature of the cardiac mechanism in anaphylaxis. Investigation of this question has been limited largely to the effect of histamine on the coronary arteries of animals and man.[18-26] The problem was reviewed by Castberg and Schwartz[27] who agreed that the cause of death in anaphylactic shock is essentially cardiac, but secondarily so, and not the result of a direct myocardial effect by the shock-producing substance. The hearts of their patients who died from allergic shock did not reveal changes of sufficient magnitude to account for death. There were only some small hemorrhages, areas of eosinophilic infiltration and myocardial edema. The lungs, however, were markedly distended without any tendency to collapse, suggesting the so-called "guinea pig" death. In the acute asthmatic attack, transient

appearance in the electrocardiogram of large P waves and RS-T segment depression was noted. In comparison, electrocardiograms of patients in allergic shock revealed similar abnormalities, that is, increase in heart rate, decreased voltage of T waves, and RS-T segment depression. Precordial leads were not taken. Changes in both groups of patients were interpreted as due to myocardial anoxia, secondary to involvement of the respiratory system, since the patients were all dyspneic, cyanotic, and wheezing during the acute reactions, as well as the frank asthmatic attack.

Since this review, there has appeared a report by Kellner, Penna, and Schweid[28] indicating that the cardiac manifestations of allergic shock in the guinea pig are the result of specific antigen-antibody reaction in the heart itself and are independent of any alteration in coronary blood flow. These investigators sensitized the hearts of guinea pigs to crystalline streptococcal proteinase and other agents and later perfused them with the sensitizing antigen. Histamine was not administered in this experiment, as had been done in the past. An attempt was made to duplicate a true antigen-antibody reaction. The sensitizing antigen caused disturbances in impulse formation and conduction in the form of ectopic beats and A-V block of varying degree. To exclude the possibility of these changes being due to variation in coronary blood flow, isolated auricular muscle from the sensitized animals was also perfused. Results obtained from these specimens devoid of blood supply were comparable to those seen in the isolated heart. Wilcox and Andrus,[18] years before, had attributed the same cardiac changes solely to decreased coronary blood flow.

The observations by Kellner and associates add another facet to the composite picture of allergic shock. It is likely that in addition to peripheral and pulmonary factors, there is a direct central or cardiac effect with the heart itself as one of the participating shock organs.

Our first case simultaneously presented features of peripheral, pulmonary, and cardiac effects. It is significant that this patient was a so-called "burnt-out asthmatic." While there had been no recent attacks it may be assumed that his bronchial tree was already sensitized to histamine, and that only a small amount was necessary to produce an exacerbation of his asthma. The precordial pain so characteristically anginal in description, the intensity of the shock state, and the electrocardiographic findings all indicate some degree of direct cardiac insult. The electrocardiographic changes seen in Fig. 1 are characteristic of acute coronary insufficiency, or subendocardial ischemia.[29,30]

The predominance of cardiac signs, clinical and electrocardiographic, in this case suggests that the basic reaction was of the "guinea pig" type. It is difficult to assess which feature played the dominant role in the production of the syndrome—the asphyxia secondary to bronchial constriction, the direct action on the coronary arteries, or the specific response of the sensitized myocardium to the injected histamine itself.

This patient recovered without sequellae, but such an acute attack may at times be fatal. The critical factor in determining survival would appear to be the state of the myocardium prior to the attack. The outcome in this particular case might have been less fortunate if there had been pre-existing coronary artery disease.

The second patient presented a somewhat different reaction. The onset of the attack was slower—the offending drug had been taken orally. The symptoms were primarily respiratory and only after a sustained and severe asthmatic attack did secondary peripheral vascular collapse occur. In the first case significant electrocardiographic abnormalities were limited to RS-T segment depression and T-wave changes; in the second case the RS-T segments remained normal and one is impressed by the abnormally tall, peaked P waves in Leads II, III, and aV_F—almost classical examples of the P-pulmonale pattern. During the acute period, the T waves were markedly lowered and diphasic. This second patient can be assumed to have reacted in the "rabbit" manner, the chief shock organ being the sensitized smooth musculature of the pulmonary arteriolar tree. As in the first case, the QRS configuration in Leads II, III, and aV_F reflect marked cardiac rotation secondary to the dynamic changes occurring within the thoracic cavity as a result of the "asthmatic" episode. The deep Q wave in Lead V_3, followed by a significant Q in V_4 demonstrates a localized "pseudoinfarct" pattern. These unusual and abnormal changes in the configuration of the precordial leads cannot be distinguished from those seen in true myocardial infarction. Electrocardiograms taken after the acute attack (Fig. 2,*B*) revealed marked regression in the amplitude of the P waves, appearance of normal T waves, a significant change in the configuration of the ventricular complexes in the precordial leads with a small r wave in V_3 where formerly a deep, wide Q wave was present, and increased amplitude of the R wave in V_4 to V_6. The possibility of a localized anterior wall myocardial infarction is extremely remote in view of the rapid disappearance of this Q.

Myers[31] has commented on this pattern of the QRS complex in the precordial leads in the uncomplicated right ventricular hypertrophy and/or dilatation occasionally seen in the asthmatic patient. These changes consist of localized decrease in the amplitude of the R wave or a QS deflection in the "transitional zone" of the precordial leads. However, application of the criteria suggested by him for interpreting such abnormal Q waves serves only to heighten the illusion of infarction in our tracing. The abnormal QS in Lead V_3 is followed by a significant Q wave in V_4, thus meeting Myers criteria for true infarction. Yet these abnormalities were considerably modified the very next day, and had disappeared a few days later. The authors feel that this localized "pseudoinfarct" pattern reflects the rotation of the cardiac vector loop posteriorly and to the left, as a probable result of changing dynamics within the chest cavity. The disappearance of the Q wave with the subsidence of the acute respiratory distress rules out the possibility of myocardial infarction having occurred.

Treatment in the "rabbit" and "guinea pig" types of reaction is similar. It includes antihistamines, epinephrine, vasopressor agents, and oxygen. If the patient remains refractory to these conventional agents the judicious and early use of intravenous hydrocortisone, 100 to 300 mg. over a six-hour period, may be life-saving.[32]

CONCLUSIONS

1. Allergic shock is due to an antigen-antibody reaction and the consequent liberation of histamine or a similarly acting substance from affected tissues or "shock organs."

2. Signs and symptoms of the shock state probably result from involvement of the myocardium, the coronary arteries, the peripheral vascular system, and the bronchopulmonary mechanism.

3. Histamine, diagnostically or therapeutically, should be avoided in patients with allergic or asthmatic histories, however remote.

4. All asthmatic or frankly allergic individuals should be questioned thoroughly in regard to drug sensitivity before any agent is administered.

5. The anaphylactoid state should be treated early and vigorously with antihistamines, epinephrine, vasopressors, oxygen, and intravenous hydrocortisone.

6. Electrocardiographic changes during allergic shock may consist of coronary insufficiency and pseudoinfarct patterns. These may be transient.

SUMMARY

Two cases of severe shock occurring in asthmatic individuals after the administration of histamine and aspirin are presented. Electrocardiographic changes in both cases during the acute and recovery phases are considered.

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TUMOR EMBOLISM OF THE LEFT CORONARY ARTERY

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CORONARY embolism, from whatever source, is a rare cause of coronary occlusion, as judged by the paucity of reports in the literature. In 1953 Cheng and associates[1] could collect only fifty such cases. The clinical diagnosis of its consequences is not usually difficult, but perhaps only in the occurrence of myocardial infarction during the course of bacterial endocarditis is embolism immediately considered as the etiologic factor, and then often hesitatingly. The following case report is to document a pathologic curiosity: coronary embolism from a bronchogenic carcinoma with resultant acute myocardial ischemia and death. The case is of interest not only because of unique pathology but also because of relatively close clinical, electrocardiographic, and pathologic study. Tumor embolism of the coronary artery system causing death has not yet been reported, to the best of our knowledge.

CASE REPORT

R. C., a 60-year-old male laborer, was well until January, 1955, at which time he noted the onset of a persistent unproductive cough and deep, aching, but inconstant, left chest pain which was aggravated by jolting or by sudden movement. From the onset of his symptoms until he first consulted a physician in October, 1955, there was a loss of 56 pounds. The patient had been a heavy smoker from adolescence, but claimed he had given up tobacco entirely ten years previously. After appropriate investigation, a diagnosis of bronchogenic carcinoma was suggested and subsequently confirmed by biopsy. The tissue report was anaplastic carcinoma. He received Cobalt 60 Beam Therapy. Subsequently he developed recurrent left pleural effusion and auricular flutter. The arrhythmia was controlled with digitalis and quinidine.

On Dec. 31, 1955, the patient was admitted to Deer Lodge Veterans' Hospital. He appeared pale and emaciated. A few small nodes were palpated in the posterior triangles of the neck. There were physical signs of fluid in the left chest and a chest x-ray revealed a homogeneous density over the greater portion of the left lung, more marked from the base to the level of the fifth rib anteriorly. There was a protodiastolic gallop. B.P. was 95/70 mm. Hg and the pulse was 90 and regular. There was clubbing of fingers and toes and a radiation dermatitis of the left chest. Hemoglobin was 66 per cent; R.B.C., 3.5 million; W.B.C., 12,500 with 86 per cent neutrophils, 12 per cent lymphocytes, and 2 per cent eosinophils. Urine was negative, sedimentation rate 70 mm. (Westergren). Sputum was negative for acid-fast bacilli.

On Jan. 5, 1956, an electrocardiogram (Fig. 1) showed sinus rhythm, QRS 0.07, flattened T_1, and inverted T_{aV4}. The patient's course was unrelentingly downhill with anorexia, weight

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loss, fever, and mental depression. On Feb. 8, 1956, severe deep-seated retrosternal pain began at noon and persisted despite analgesics. The pain was accompained by vomiting and profuse sweating. By 2:00 P.M. the pulse was rapid and thready, and B.P. 60/0 mm. Hg. The patient was in a state of shock. At 4:00 P.M. an electrocardiogram was taken (Fig. 2), which revealed marked S-T depression in standard and left precordial leads. At 6:30 P.M. the patient expired.

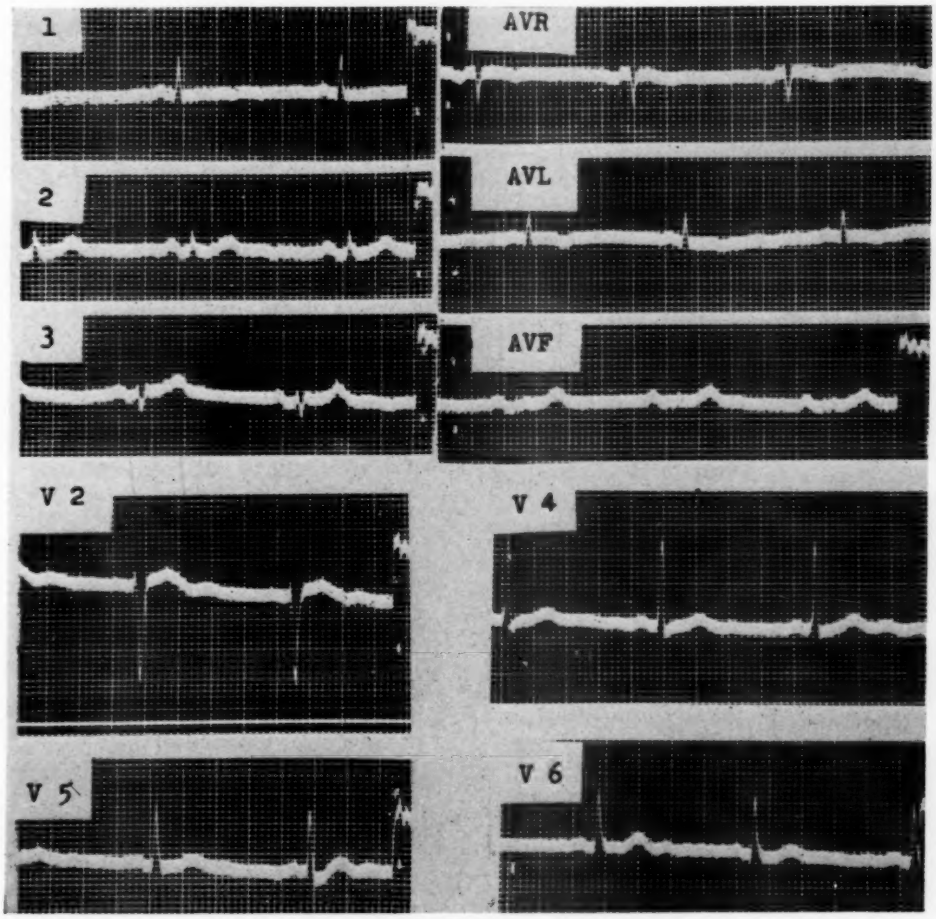

Fig. 1.—Electrocardiogram taken Jan. 5, 1956, showing flattening of T waves in Lead I and inversion in aV$_L$.

Necropsy Findings.—Necropsy was performed thirteen hours after death. Aside from a moderate degree of emaciation, the external appearance was not remarkable.

Pertinent findings were confined to the thorax. The left lung weighed 910 grams. Centered about the superior division of its upper lobe bronchus was a large, hard yellowish-gray mass extending laterally into the left upper lobe with areas of necrosis and atelectasis of the adjacent noninvaded lung parenchyma. Medially, the growth extended into the mediastinum, where it was confluent with grossly enlarged, firm lymph nodes and was directly apposed to the ascending aorta and the pulmonary artery. Inferomedially the tumor mass was firmly attached to the anterior wall of the left atrium.

On tracing the left upper lobe bronchus, it was found patent up to 5 mm. past its division, at which point the superior division disappeared into necrotic tumor tissue. The right lung

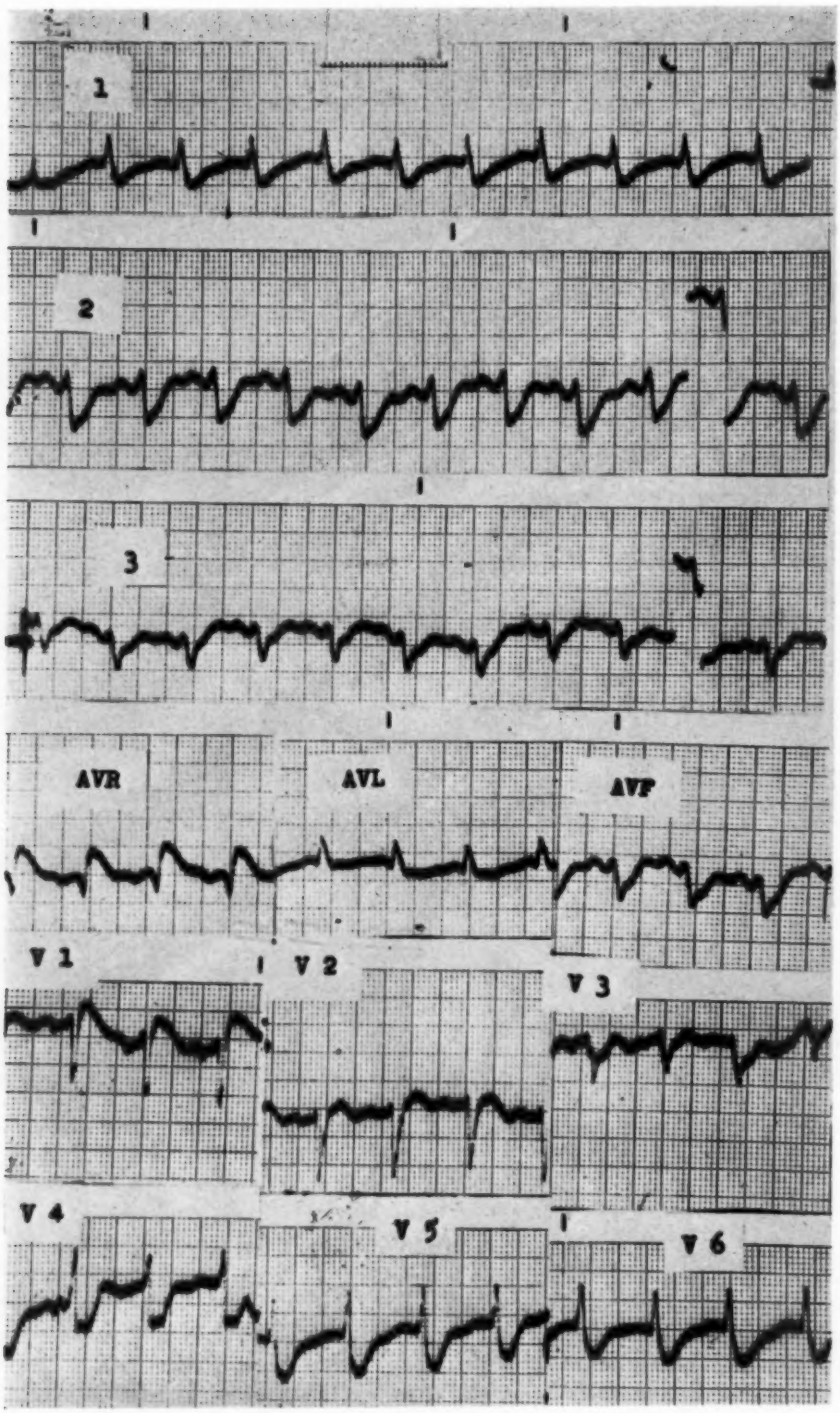

Fig. 2.—Electrocardiogram taken Feb. 8, 1956,—four hours after the onset of retrosternal pain—showing marked S-T depression in Leads I, II, III, aV_F, V_3, V_4, V_5, and V_6 and S-T elevation in Leads aV_R and V_1.

weighed 840 grams, appearing more solid than usual and exuding frothy, pinkish-brown fluid on serial section. A bilateral hydrothorax was present with 640 c.c. of clear, straw-colored fluid on the right and 200 c.c. on the left.

The heart weighed 600 grams, and showed moderate dilatation of all chambers. A remarkable feature was a hard, white thickening of the epicardium up to 3 mm. around the base of the left ventricle. This tumor tissue was continuous with the main mass and extended for a distance of 2½ cm. down the surface of the left ventricle, surrounding the proximal third of the left anterior descending coronary artery.

On opening the left atrium, the anterior wall was invaded by tumor tissue which had eroded the endocardial lining, forming an intraluminal fungating mass 1½ cm. in diameter. The myocardium of the remaining chambers was not remarkable except for some pallor and a suggestion of fine diffuse fibrosis.

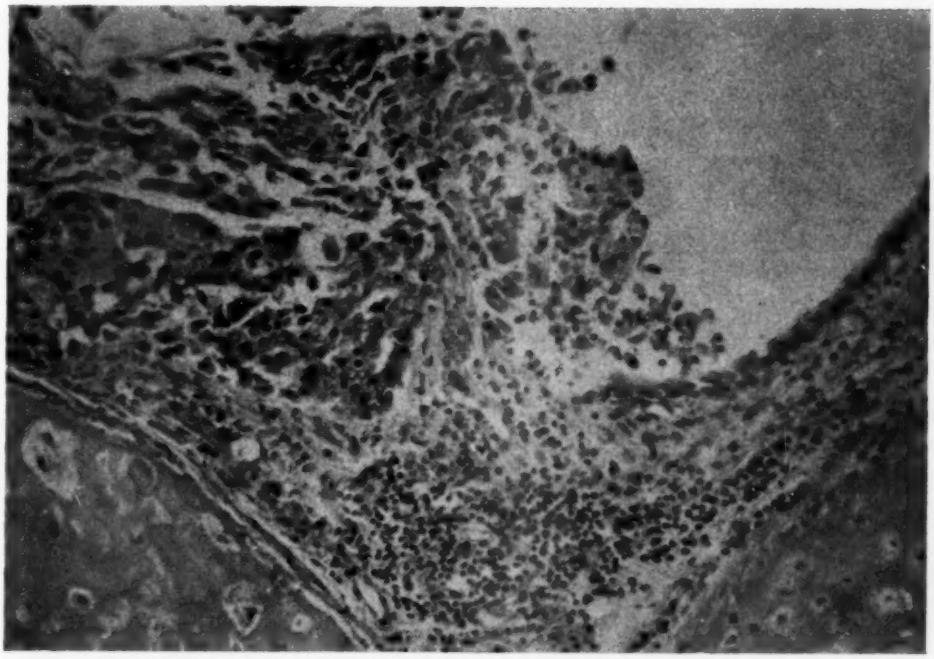

Fig. 3.—Left upper lobe bronchus showing cartilage with overlying normal mucosa on the right adjacent to epidermoid carcinoma on the left. Hemalum-Phloxine-Saffron stain × 200.

Microscopically, an epidermoid carcinoma was seen involving the left upper lobe bronchus and surrounding lung parenchyma (Fig. 3), the wall of the left atrium (Fig. 4), and the epicardium on the upper portion of the left ventricle. The tumor was composed of irregular sheets of moderately anaplastic and pleomorphic cells with large vesicular nuclei containing single nucleoli. In some areas there were intercalated discs with intercellular bridges giving a prickle-cell appearance.

Although the proximal portion of the left coronary artery was surrounded by tumor, there was no compression or direct invasion of the wall. However, the lumen of the anterior descending branch of the left coronary artery was occluded by a mass of pleomorphic squamous cells identical to those seen in the primary tumor (Figs. 5 and 6). Sections of the left ventricle showed focal cloudy swellings of the myofibrils with some loss of striations.

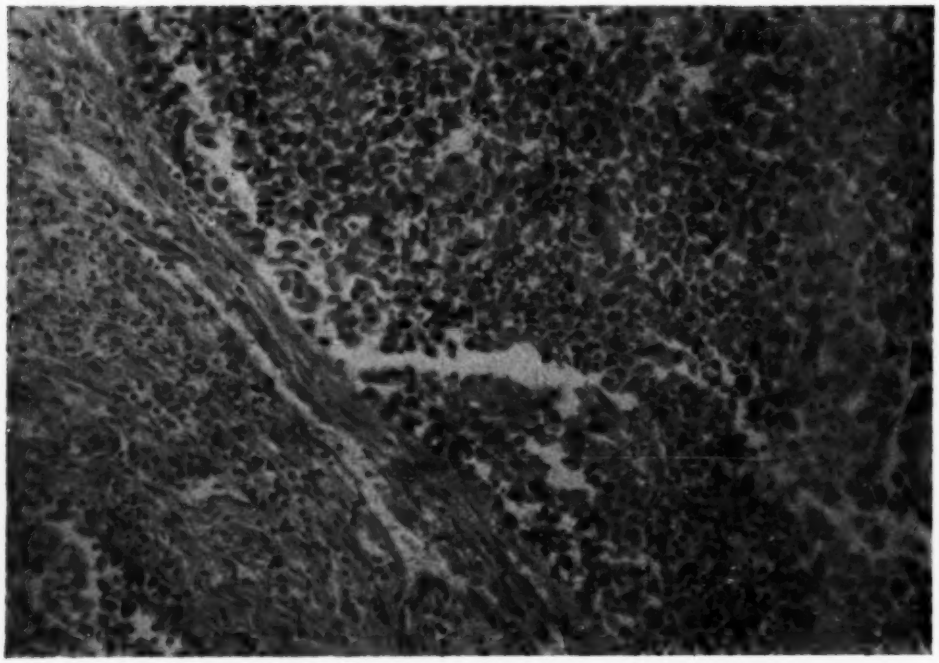

Fig. 4.—Wall of left atrium showing massive invasion and disruption of myocardial fibers by tumor cells. Hemalum-Phloxine-Saffron stain × 200.

Fig. 5.—Cross section of left anterior descending coronary artery showing lumen occluded by tumor cells. Hemalum-Phloxine-Saffron stain × 90.

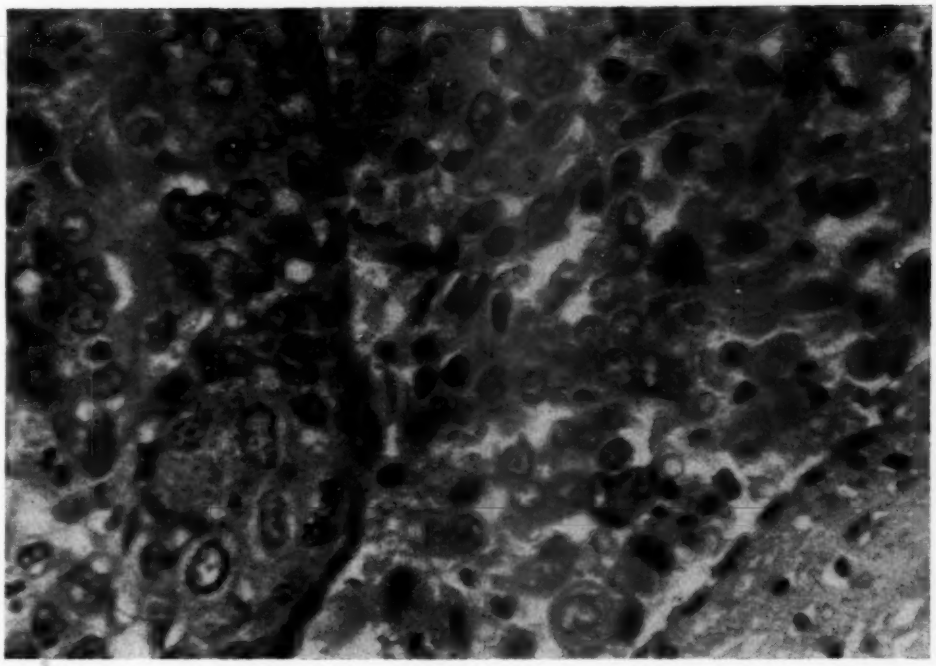

Fig. 6.—Higher power view of Fig. 5 showing edge of intimal layer in the right lower corner and lumen filled by pleomorphic tumor cells Hemalum-Phloxine-Saffron stain × 400.

DISCUSSION

Although external coronary compression by tumor has been described,[2] the only previous case of actual tumor embolism of the coronary arteries known to us was reported by Thompson and Evans,[3] in 1930. Their case concerned a 25-year-old man with a malignant teratoma involving both testes. The patient died of the effects of a tumor embolus to the right middle cerebral artery. At necropsy there was, in addition, a tumor metastasis on the right wall of the interatrial septum, a portion of which was protruding through a patent foramen ovale. A metastasis in the wall of the left ventricle projected into the cavity of the left ventricle and was associated with a mass of tumor lying free within the left ventricle. Both coronary arteries contained tumor emboli, but the report did not state whether or not the coronary arteries were completely occluded by tumor. In the case presently under discussion, metastases were found only in the heart, and although the patient was previously seriously ill, the immediate cause of death was clearly the coronary occlusion. It is considered that the relatively short period between the time of the onset of pain and the patient's death (six and one-half hours) explains the absence of myocardial infarction.

SUMMARY AND CONCLUSIONS

A case has been described wherein a primary carcinoma of the left upper lobe bronchus invaded the left atrium of the heart with subsequent tumor embolization of the anterior descending branch of the left coronary artery.

Clinical and electrocardiographic evidence indicated that death was due to effects of the embolism, although death supervened before frank myocardial necrosis could occur.

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George Lyman Duff

The officers and directors of the American Society for the Study of Arteriosclerosis report with regret the untimely death of Dr. George Lyman Duff, late Professor of Pathology and Dean of the Faculty of Medicine of McGill University, Montreal, Canada. Lyman Duff was a founding member and a past president of the Society. He was admired and respected by all and loved by those who knew him. He made many basic contributions in the fields of cardiovascular diseases and pancreatic physiology. His clear thinking and his precise terminology will always give substance to the group. Because of love for him, the Society will establish its first Annual Memorial Lectureship and call it the George Lyman Duff Lecture.

CONGESTIVE HEART FAILURE IN POSTMENOPAUSAL MUSCULAR DYSTROPHY: MYOSITIS, MYOCARDITIS, THYMOMA

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THIS communication concerns a death from congestive heart failure during the course of postmenopausal muscular dystrophy. At autopsy there was a granulomatous myositis of the skeletal and heart muscle, a benign thymoma, and an acute pericarditis.

CASE REPORT

A postmenopausal 64-year-old white widow was admitted to the hospital for the fourth time on Jan. 19, 1954, with a chief complaint of dyspnea, orthopnea, and paroxysmal nocturnal dyspnea for two weeks. There had been progressive swelling of both legs for two years and marked generalized weakness for seven weeks.

She had been perfectly well until May, 1952, at which time an abdominoperineal resection for carcinoma of the rectum was performed. The postoperative course was stormy. There was a deep wound abscess with bacteremia and metastatic abscesses. The patient also developed bilateral deep and superficial phlebitis of the legs. When discharged from the hospital on July 31, 1952, she was afebrile and complained only of edema of both legs. One month after discharge from the hospital she developed marked weakness of the legs and had difficulty in arising from the sitting position. This weakness was transient and lasted only a few weeks. Toward the end of August irregular fever developed. In September, 1952, the patient presented herself with a large left perirenal abscess. Incision and drainage was followed by uneventful recovery.

From September, 1952, until Oct. 16, 1953, she felt well. The edema of both legs was controlled with elevation of the foot of the bed at night and the wearing of elastic stockings while ambulatory. The colostomy functioned well and the patient was able to lead her normal life. On Oct. 16, 1953, the patient tripped on a curb while crossing the street and fractured the second left metatarsal. A walking cast was applied and, despite the weight of this encumbrance, the patient was able to get about doing her own housework and neighborhood shopping. The cast was removed on Nov. 15, 1953. Fifteen days later, the patient developed a severe cough with an oral temperature of 99° F. She looked acutely ill and showed signs of moderate weight loss. There was recurrence of the weakness of the hands and legs initially manifest transiently in August, 1952. The patient stated that she had great difficulty in getting out of a chair and also difficulty in turning doorknobs. Physical examination revealed many râles in the left lower lobe and marked edema of the legs and thighs. The heart was regular, not enlarged, the sounds were of normal quality, and there were no murmurs. On Chloromycetin and Brown's mixture the cough cleared up in several days. Two days later she was much better, but the weakness of both hands and legs was still present. Her temperature was still 99° F. by mouth and a few râles were heard at the left base. Chloromycetin was continued in a smaller dose. By December 7 her lungs were completely clear. However, her hands were no stronger and her generalized weakness was much more pronounced. Neurologic examination at that time revealed

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a broad-based "Marche a petit pas" gait. There was marked atrophy of the deltoids, sternocleidomastoids, and calf musculature. There was moderate atrophy of the temporals, supraspinati, which was more marked on the left, the adductors of the thighs, and all of the long back musculature. There was slight but definite atrophy and weakness of almost all other muscles. There was no recovery of strength after a period of rest, and repeated motions did not lead to pathologic fatigue. There was no diplopia nor was there any fatigue on continued talking or on swallowing. She was unable to raise her arms above the head and also could not arise from a prone position on the floor. No fasciculations were noticed and there was no evidence of myotonia. The deep tendon reflexes were not elicited in the upper extremities. They were brisk in the lowers. Plantar reflexes were normal. There were no pathologic reflexes. No disturbances of pain, touch, vibratory, position, or temperature sensations could be elicited. The cranial nerves were intact. There was no evidence of an organic mental syndrome.

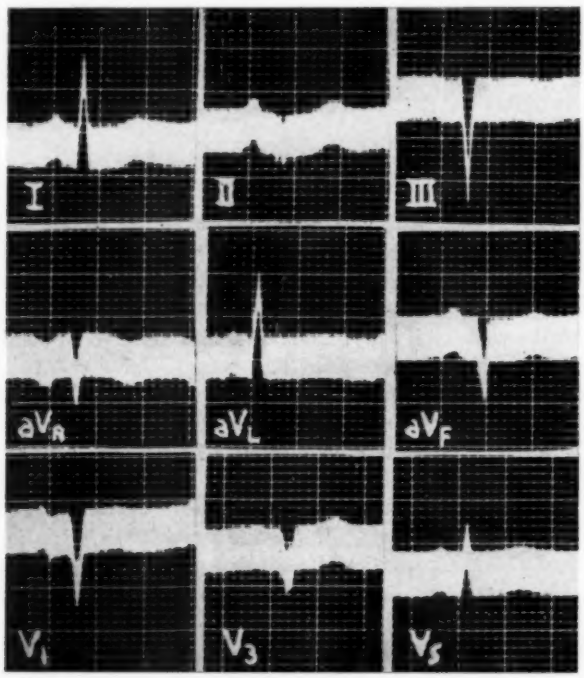


Fig. 1.—Electrocardiogram. Standardization 0.5 cm. = 1 mv. for the V leads.

The diagnosis at this point was postmenopausal muscular dystrophy, postphlebitic edema of the legs, and convalescence from bronchopneumonia. On December 17, eighteen days after the onset of the illness, the patient required an attendant to help her get in and out of a chair, and to get dressed and undressed. She was almost completely helpless. Several injections of prostigmine were of no benefit. Early in January, 1954, mercuhydrin was given with marked diuresis and definite improvement of dyspnea which had developed rather suddenly. There was only slight decrease in the edema of the legs. On January 17 there was marked dyspnea and orthopnea. Mercuhydrin was of transient benefit. Dyspnea, orthopnea, and paroxysmal nocturnal dyspnea were present. Physical examination revealed evidence of effusion in the right base. There was no distention of the neck veins.

The patient was admitted to the hospital on Jan. 19, 1954, because of marked dyspnea, orthopnea, severe generalized weakness, and pitting edema up to the lower thoracic region. She was afebrile. The lungs were clear. The heart was not enlarged. The rate was regular as was the rhythm. There were no murmurs. X-ray examination of the chest showed a moderate amount of fluid in both pleural cavities. The electrocardiogram (Fig. 1) revealed a QS in V_3. This was thought to be evidence of an anterior wall infarct. The patient was given digitalis

and mercurials with rather rapid disappearance of the fluid and moderate improvement in the dyspnea. On the afternoon of January 22 a pericardial friction rub was heard, and at 1 A.M. on January 23, the patient was found dead.

Autopsy Report.—

Significant findings: There were 200 c.c. of fluid in each pleural cavity. Aside from a pinkish frothy fluid exuding from the cut surfaces of the lungs these organs were normal. Retrosternally there was a mass overlying the great vessels at the level of the manubrium. This mass was firm, well encapsulated, yellow-gray in color, and measured 4.8 cm. by 2.5 cm. The pericardial sac contained 50 c.c. of purulent fluid. The heart weighed 300 grams and was covered with fibrinopurulent material. All valves and the entire endocardium were normal. There was no chamber enlargement. The walls of the various chambers were of normal thickness. On section the myocardium was mottled reddish-brown and yellow. The coronary arteries showed very little sclerosis and the ostia were widely patent. The aorta showed some atherosclerotic plaques. The intercostal, rectus, psoas, and quadratus muscles had a pale brown color and were diffusely streaked by gray tissue.

Genitourinal system: The right kidney was normal. The left kidney had a deep gray scar in the cortex. The capsule was densely adherent. The cut section of the kidney showed normal architecture and the pelvis and calyces were normal. The urinary bladder was normal.

Microscopic Examination.—

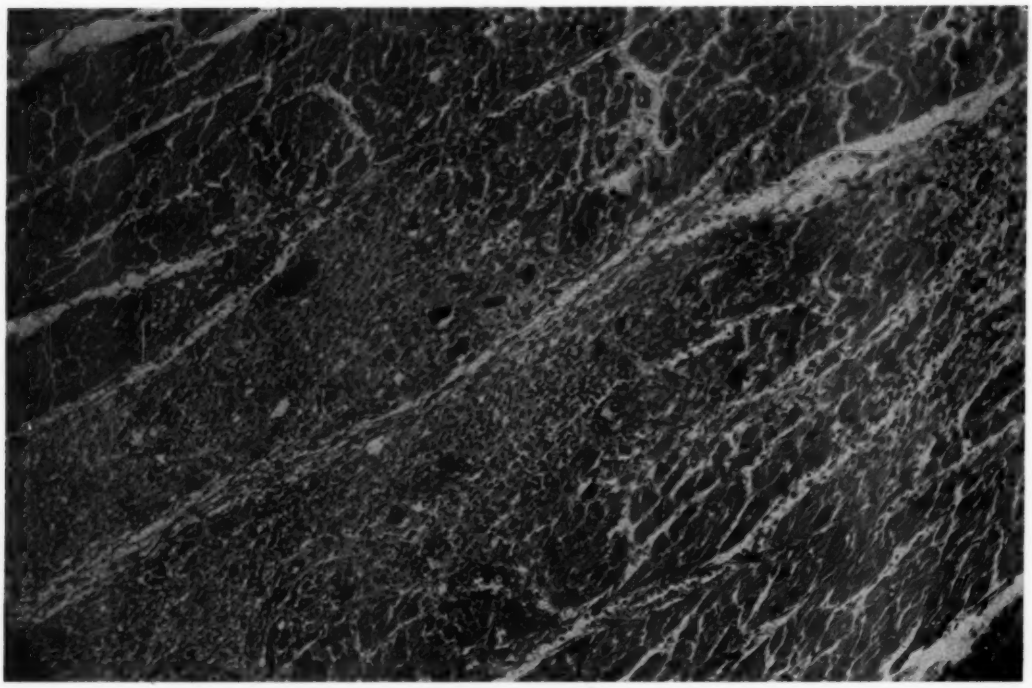
Thymus: There were small islands and large sheets of cells which had large, medium-sized vesicular nuclei with acidophilic scanty cytoplasm. Interspersed among these cells there were also some with small, dark-staining nuclei whose cellular outlines were indistinct. Dense hyalinized fibrous connective tissue septa divided these sheets of cells into nodules.

Heart: The myocardial fibers were hypertrophied. Large areas of the muscle were either infiltrated or replaced by a granulation tissue which was partly dense and fibrotic, or which was made up of fibroblasts and infiltrated with lymphocytes, polymorphonuclear leukocytes, cells with large vesicular nuclei and indistinct cellular outlines, and giant cells with a pale eosinophilic cytoplasm and multiple oval-shaped vesicular nuclei (Fig. 2). These changes were seen throughout the myocardium. The endocardium was intact throughout. The epicardial fatty tissue was edematous and infiltrated with inflammatory cells, chiefly polymorphonuclear leukocytes. Its surface was covered by a layer of fibrin in which were enmeshed polymorphonuclear cells in large numbers, red blood cells, and cellular debris forming a layer of eosinophilic material.

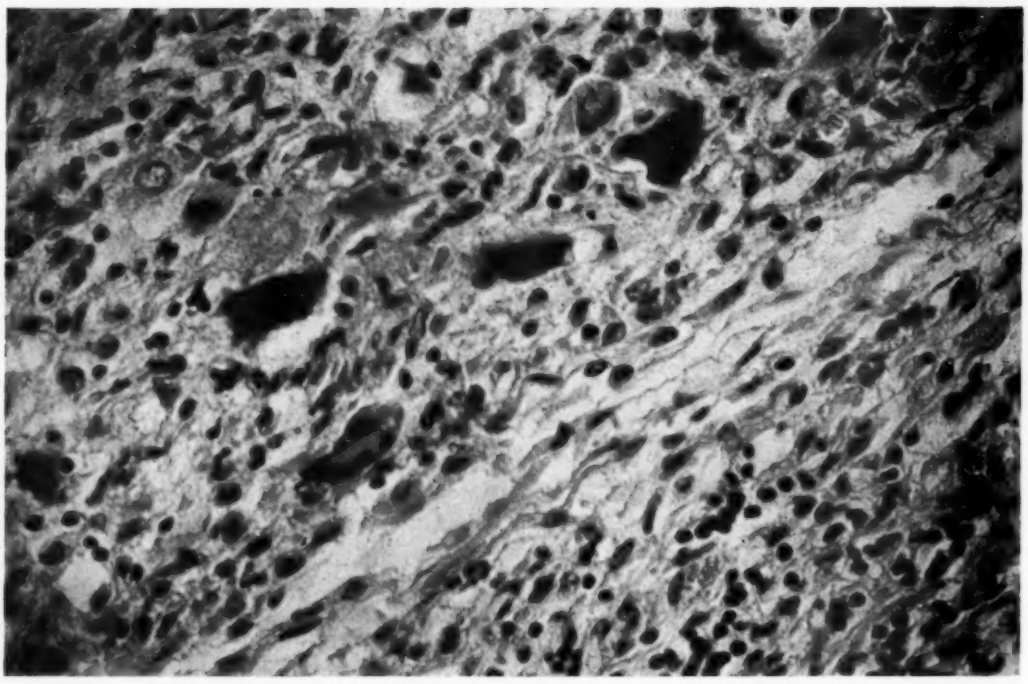
Muscle: Sections taken from psoas (Fig. 3), quadratus, and intercostal muscles revealed a similar histologic picture. The fibers were separated by an infiltrate made up of serum and containing various inflammatory cells. Areas of fibroblastic proliferation were frequently evident, and here similar inflammatory cellular infiltration was present consisting of lymphocytes, plasma cells, polymorphonuclear leukocytes, and multi-nucleated giant cells. Many of the muscle fibers were compressed, atrophied, or fibrosed. These changes were identical to those observed in the heart muscle.

DISCUSSION

There is a striking clinical and pathologic resemblance between this case and many of those[1-3,11] reported as isolated myocarditis (Fiedler's type). Indeed our patient would have been reported as isolated myocarditis had skeletal muscle not been examined at autopsy. Interestingly there is not a single report in the entire medical literature on the findings in skeletal muscle of patients who have had Fiedler's myocarditis. Since weakness is a prominent sign and symptom of congestive heart failure and maybe a major manifestation of Fiedler's myocarditis,[2] the possibility exists that in chronic disease with marked weakness, the skeletal muscle is suspect, whereas in an acute illness with congestive heart failure attention is focussed solely on the heart. Congestive heart failure is a rare[4-6] but well-known development in the juvenile form of progressive muscular dystrophy.



A.



B.

Fig. 2.—*A*, Myocardium showing inflammatory infiltrate, giant cells, and granulation tissue. *B*, High power from center of *A* showing giant cells.

The diagnosis of muscular dystrophy and that of myasthenia gravis are based on clinical findings, there being no pathognomonic pathologic picture. Since this patient clinically had muscular dystrophy the pathologic findings must now be included among those which can be found in this disease. The addition of the granulomatous myositis to the constellation[7-10] of pathologic findings previously recognized as occurring in muscular dystrophy now makes these findings identical with all of those which have been found in isolated myocarditis,[3] including the terminal pericarditis.[11] The pathologic findings in myasthenia gravis[12] may also include granulomatous changes in skeletal and heart muscle, although, despite extensive myocardial changes, clinically significant heart disease[12-14] does not occur in this condition. Boman[15] reported one patient with myasthenia gravis who died in congestive heart failure but at autopsy there was advanced arteriosclerotic heart disease with coronary thrombosis and myocardial infarction. No myositis was found.

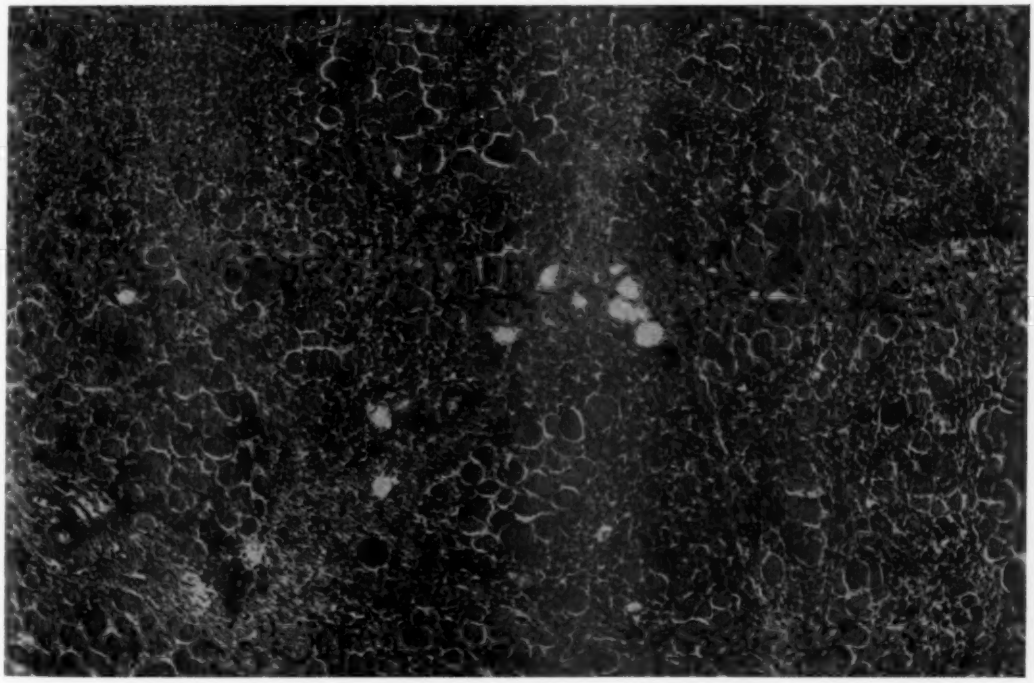


Fig. 3.—Psoas muscle showing same changes as in Fig. 2.

A thymoma[16,17] is found in 15 per cent of patients who have myasthenia gravis and 75 per cent of thymomas occur in patients who have myasthenia gravis. There is no association of thymoma with any other disease entity.[16-18] It has never been reported in isolated myocarditis or in muscular dystrophy.

Myocarditis of varying extent is found in a wide variety of infections,[3,19,20] and myositis of skeletal muscle[21] is found under a very similar group of circumstances. Although the case under discussion had bacteremia with metastatic abscesses, the last clinical evidence of infection disappeared thirteen months before the onset of the terminal illness. Autopsy confirmed the clinical im-

pression of no residual focus of infection. The carcinoma had apparently been entirely eradicated.

The surprising and unusual mixture of clinical and pathologic findings in the present case casts some doubt on the validity of our present classification of the diseases of striated muscle.

SUMMARY

A 64-year-old white postmenopausal widow developed muscular dystrophy and congestive heart failure. There was a terminal pericarditis. Autopsy revealed granulomatous myositis of all striated muscle, pericarditis, and a thymoma. Attention is drawn to the clinical and pathologic resemblance of isolated myocarditis (Fiedler's type) to the heart disease of muscular dystrophy. Similar granulomatous myositis is occasionally found in myasthenia gravis. A thymoma has never before been reported in any generalized disease except myasthenia gravis.

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